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Fallacy of Per-Weight and Per-Surface Area Standards, and Their Relation to Spurious Correlation

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BOTH IN PHYSIOLOGY and clinical medicine, the results of some measurements, for example, of oxygen consumption and cardiac output, are commonly expressed as per-weight or per-surface area ratios. Normal standards for both these variables, in fact, have been constructed on this basis; and as more similar variables come to be measured on the human being, the number of standards constructed and of results reported in this way, may be expected to increase. It seems useful to point out, therefore, that such standards are theoretically fallacious, and in practice (except under very special circumstances discussed below) misleading. The fallacy involved may be considered as a special case of that well known to statisticians as the spurious correlation of indices.

The writer first became aware of this situation when constructing some new standards for cardiac output in man (1). A cursory review of the literature revealed that the consequences of using these ratios were not at all widely realized. Examples immediately came to light where investigators had drawn positive conclusions not justified by their data, had been confused by a seemingly uninterpretable phenomenon in their results, had proposed a less effective and more biased normal standard in preference to a more effective and less biased one, had reduced a correlation between two physiological functions from a very high to a medium value, and had invented a new clinical syndrome. All these events were wholly or in major part due to the incautious use of ratios. Examples of each are given in the second half of this paper, by way of making the point that the theoretical discussion which now follows has a severely practical upshot. The examples concern cardiac output, basal metabolism standards in adults and children, the relation of body build and oxygen consumption, and the choice of plasma volume standards in man; and in the dog, the statistics of renal plasma flow and glomerular filtration rate.

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The theoretical argument is such that the reader whose knowledge of statistics extends merely to the understanding of the words mean, ratio, standard deviation, correlation coefficient and regression line will be able to follow it in detail.

THEORETICAL

Error of the Ratio Standard. The subject can most easily be introduced by reference to cardiac output data on 50 healthy young men reported elsewhere (1). Figure 1 shows the stroke volume of the heart plotted against body weight in the human. Now the use of the ratio per-weight standard implies that in the normal person, the stroke volume is proportional to the weight; in fact that the expression

$$\text{Str. vol.} = \text{k. wt.} \qquad (A)$$

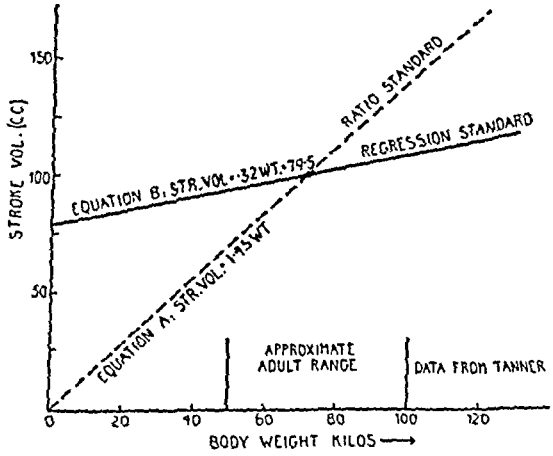

Fig. 1. RELATION of stroke volume of the heart and body weight.

holds good over the range of values of weight for which the standard is used; that is, all normal adult values. The constant k is determined by the mean values of the series of data on which the standard is founded. Thus the line in figure 1 marked *Equation A* passes through the point of the two means, and by virtue of the form of the equation, through the origin also. If this line were really a newly constructed per-weight standard, we should judge any given stroke volume as normal or abnormal according to how far away from the line our value fell; that is, how far from the figure 1.45 cc/kg. the stroke volume was. This is in fact current clinical practice, using either the per-weight or per-surface area standard. Now actually, this expression by no means represents the mathematically 'best' or 'true' relation between stroke volume and weight. The best relation is that given by the regression equation (we are assuming rectilinearity of regression, which is justified at least as a first approximation) and this equation is.

$$\text{Str. vol. (cc.)} = .32 \text{ wt. (kg.)} + 79.5. \qquad (B)$$

This is the line called *Equation B* in figure 1, and it will be seen that it only coincides with that of *Equation A* at one point, the means. The ratio standard implies that the line of regression, that is the line fitting most closely the actual data, passes through the origin, and it is here that the fallacy lies. The assumption is unwarranted and obviously untrue, and results from an unjustified extension of the linear relationship into regions where it certainly does not apply, outside the adult range. The somewhat speculative argument that a person of no weight has no stroke volume is quite beside the point.

The difference in normal standards constructed from *equations A* and *B* is considerable. *Equation B* should be our proper standard, and it can be seen from figure 1 that a heavy man of 90 kg. will be given by the ratio per-weight standard a 'normal' stroke volume which is too high, by as much, in this instance, as 21 per cent. It is, indeed, at least partly this fallacious standard which has given rise to the idea that heavy men have relatively low stroke volumes; Starr's statement that "we found that the lowest values were frequently obtained on subjects definitely overweight" (2). Light people, on the contrary, will have too high an output as judged by the current standard, which gives them too low normal values. The error is about 22 per cent for a person of 50 kg. Consequently thin people have been said to have excessively high cardiac outputs and indeed some of the cases described by Starr and Jonas (3) as 'essential hyperkinemia', not those who had very elevated pulse rates, may have been suffering from no more formidable a disease than statistical artefact. The per-surface area standard leads to a similar, though not such a numerically large error.

We must now examine the matter in rather more detail. The actual regression equation, such as B, using X and Y as raw scores, b as the regression coefficient and a as the value of Y when $X = 0$, is

$$Y = bX + a. \qquad (C)$$

This line will only coincide with the ratio line $Y = kX$ when the two regression coefficients, b and k, are equal, and when a is zero. This condition can be conveniently put in another form for those who are more familiar with the terminology of correlation coefficients. If M_x and M_y are the means of the x and y variables, and r is the coefficient of correlation between them, the regression *equation C* becomes

$$Y = \frac{r\sigma_y}{\sigma_x} X + \left(M_y - \frac{r\sigma_y}{\sigma_x} M_x\right). \qquad (C1)$$

This line will only pass through the origin when the term in the bracket is zero, i.e. when

$$M_y = \frac{r\sigma_y}{\sigma_x} M_x$$

i.e. when

$$\frac{r\sigma_y}{M_y} = \frac{\sigma_x}{M_x}. \qquad (C2)$$

The coefficient of variation, v, is given by

$$v = \frac{100\sigma}{M}$$

so that the condition above (*C2*) reduces to

$$rv_y = v_x$$

or

$$\frac{v_x}{v_y} = r. \qquad (D)$$

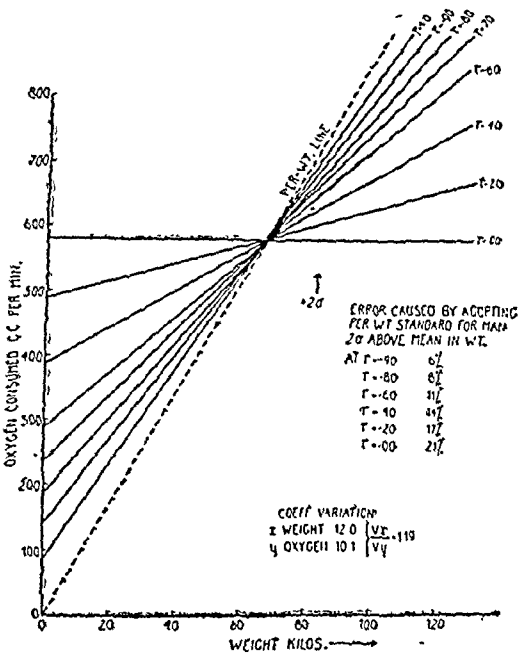

Fig. 2. RATIO LINE and regression lines to show the varying values of r_{xy}.

This, then is the condition that the regression line should be coincident with the ratio line (since both lines go through the mean always). Figures 2, 3 and 4 illustrate this. In figure 2 data are oxygen consumption per minute following a standard exercise, and body weight, on 74 subjects (4). The dotted line is the per-weight line, and the solid lines show the effect of various values of r between weight and oxygen consumption (the one actually observed being 0.27). In this example the ratio of the coefficients of variation is 1.19, and since r can never be this large, no regression line can exist which would coincide with the ratio-line. But as r increases, the lines do get closer, and the error caused by the use of a ratio standard gets less. The percentage errors for a man of 2σ above the mean in weight are shown for various values of r. For

the real data, supposing the ratio line had been a standard, the *actually* best prediction for such a man would have been *called* about 15 per cent too low.

The actual amount by which the regression equation value differs from the ratio equation value can be very simply obtained from the equations of the two lines A and C. Thus

$$\begin{aligned} Y_{\text{regr.}} - Y_{\text{ratio}} &= bX + a - kX \\ &= (b - k)X + a \end{aligned} \qquad (E)$$

When $b = k$, the difference between the equations is independent of X and equal to a; the lines are, in fact parallel. Under any other circumstances however, $Y_{\text{regr.}} - Y_{\text{ratio}}$ is dependent upon the value of X, and gets progressively larger numerically as X departs more from its mean value. The lines, coincident at the mean, diverge more and more as we go away from the mean. The ratio equation gives Y/X, stroke volume/wt., as a constant k, but the regression equation leads to

$$\frac{Y}{X} = b + \frac{a}{X} \qquad (E1)$$

that is, stroke volume/wt. not constant, but inversely proportional to the weight. In actual figures, in the data of *equation B*

$$\frac{\text{Str. vol.}}{\text{wt.}} = .32 + \frac{79{\cdot}5}{\text{wt.}}. \qquad (E2)$$

In other words, and in general, there *actually* exists a correlation between y/x and x, and this can be shown to be positive if $\frac{v_x}{v_y} < r$ and negative if $\frac{v_x}{v_y} > r$. The ratio standard ignores the existence of this correlation.

Relation of the Ratio Standard to Spurious Correlation. This is the crux of the matter. This correlation is merely a special example of a class of correlations very well known to statisticians and described originally by Karl Pearson in 1897, under the heading of 'spurious correlation between indices' (5). The general formula for the coefficient of correlation between two indices formed from the variables 1, 2, 3, 4 (i.e. indices $\frac{1}{3}$ and $\frac{2}{4}$) was shown by Pearson to be

$$r = \frac{r_{12}v_1v_2 - r_{14}v_1v_4 - r_{23}v_2v_3 + r_{34}v_3v_4}{\sqrt{v_1^2 + v_3^2 - 2r_{13}v_1v_3}\sqrt{v_2^2 + v_4^2 - 2r_{24}v_2v_4}} \qquad (F)$$

For the case y/x and $z/1$, variable 4 is a constant, $v_4 = 0$ and we have

$$\begin{aligned} r &= \frac{r_{12}v_1v_2 - r_{23}v_2v_3}{\sqrt{v_1^2 + v_3^2 - 2r_{13}v_1v_3}\sqrt{v_2^2}} \\ &= \frac{r_{12}v_1 - r_{23}v_3}{\sqrt{v_1^2 + v_3^2 - 2r_{13}v_1v_3}} \end{aligned} \qquad (G)$$

and for our particular case, which is y/x and x, variable 2 = variable 3, and we have

$$r = \frac{r_{12}v_1 - v_2}{\sqrt{v_1^2 + v_2^2 - 2r_{12}v_1v_2}} \qquad (H)$$

Thus *expression H* actually measures the degree of departure of the ratio per-weight standard from the true regression standard, in given circumstances of v_x, v_y and r_{xy}. It is, for example, zero when the two standards coincide. In passing, we may note that this expression reduces, if x and y are uncorrelated, to

$$\frac{-v_2}{\sqrt{v_1^2 + v_2^2}} \qquad (I)$$

and this further reduces to the value $-.71$ if $v_x = v_y$. (This is the figure for our special case corresponding to Pearson's well known figure of 0.5 for the general one).

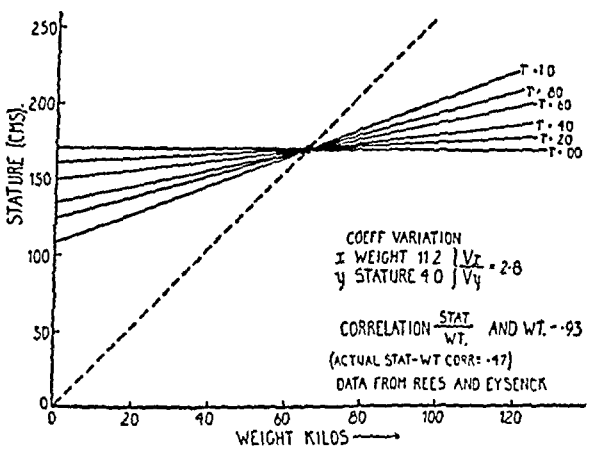

Fig. 3. To show difference between ratio and regression lines when $v_I/v_y > 1$.

In figure 2 the correlation between O_2/wt. and wt. for the actual data is

$$\frac{0.27 \times 10.1 - 12.0}{\sqrt{10.1^2 + 12.0^2 - 2 \times .27 \times 10.1 \times 12.0}} = -0.694$$

Figure 3 illustrates an even more marked case. (The data have for convenience been taken from Rees and Eysenck's study of 200 subjects (6), the present graphs being constructed only for the present occasion: the paper quoted has nothing to do with this fallacy.) Here the stature/wt. and wt. correlation is -0.93, largely because the value of v_x is so much greater than v_y. If the dotted line here represented a standard, that standard would be wildly wrong.

In all these illustrations, the correlation of y/x and x was negative; that is, heavy men were given too high a standard and their 'true' value would thus be said to be too low. With weight as the x-variable, it is rather hard to find an example of the opposite situation, but a somewhat artificial one, be-

tween age and weight, is shown in figure 4 (6). Here v_x is less than v_y and for high correlations of weight (x) and age (y), one would be led to a ratio standard of age for weight where heavy men would be given too low a standard for age. (Such an error introduced into our reckoning of age would lead to the social situation wherein the heavier a man was the younger he would be reckoned, and the lighter, the more aged; the effects on differential mortality from the behavior following such an assumption, and the activities of food firms, can well be imagined; but the example is hypothetical.) For low values of the age-weight correlation, the relation of ratio standard to true standard is reversed, and the two coincide at $r = 0.55$. Since in the actual data the age-weight correlation was zero, the (spurious) correlation of age/wt. and wt. is $-.48$.

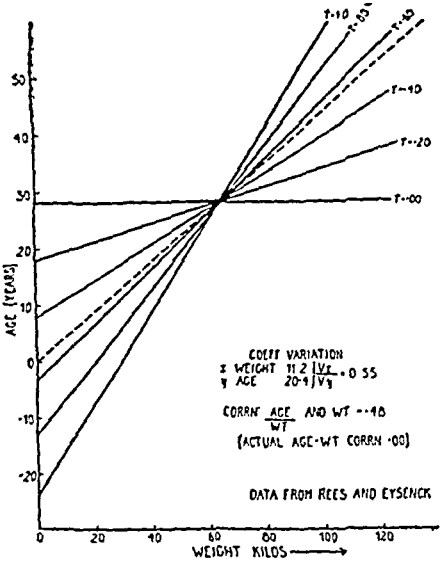

Fig. 4. To show difference between ratio and regression lines when $v_I/v_y < 1$.

EXAMPLES

Basal Metabolism

Adults. The first example of the use of fallacious standards concerned cardiac output and has already been given. That the per-weight or per-surface area standards for this variable are erroneous will not come as any particular shock to the majority of readers, who will have had no direct experience of the use of cardiac output figures. But nearly all must have used the per-surface area standards for basal metabolism and the reader must have had in mind from the beginning a query as to the fallacy in this case. The per-surface area standard is widely used, and appears to be reasonable. It is true that the original standards proposed by Harris and Benedict (7) were regression

ones, for the authors of this classical monograph were very well aware (p. 151) of the fallacy considered here, but Berkson and Boothby (8) showed that the per-surface area standard predicted as well as, or at any rate, not demonstrably worse than, regression standards of the Harris-Benedict type, for their Mayo Clinic data. The reason for this is soon discovered: the oxygen consumption-surface area relationship just happens to come very near satisfying the conditions given above for the ratio and regression standards to coincide. We cannot illustrate this for the data Berkson and Boothby actually tested since they do not give the necessary statistics. But Harris and Benedict give the following figures for 136 male subjects: coefficient of variation of surface area 8.89, of heat production 12.54; correlation coefficient between these two

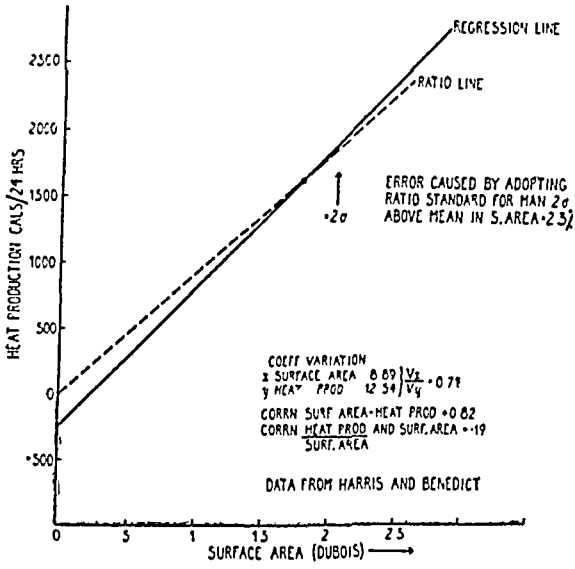

Fig. 5. RELATION BETWEEN the regression and ratio standards for basal metabolism.

variables, .82. For these figures, referring to *equation D*, $\frac{v_x}{v_y} = 0.71$ and this value is not very different from r. From *equation H* with variable 1 as y and 2 as x, we find that this measure of the difference between the two standards gives us a correlation of Heat prod/S. area and S. area of only +.19. This difference is too small in relation to the variability of the measurement itself to affect the predicted result. Figure 5 illustrates this. For a man 2σ above the mean in surface area, this difference is only 2.3 per cent of the man's measurement; and the standard deviation of a single individual from day to day about his mean is 3.5 per cent, and of a series of individuals of the same age, 5.8 per cent (9). Galvao's two series (10, 11) both separately and combined, have O_2/S. area ratio lines even more closely approximating the regressions.

In short, the oxygen consumption ratio standard *is*, very nearly, the special case where ratio and regression lines coincide. Even so, because the

lines do not *exactly* coincide, a large man has a very slightly greater chance of being called hyperthyroid than a small man, and this purely artefactually.

Children. In children's standards, however, the effect seems to be important, presumably because the variability of weight and surface area for some single-year age groups considerably exceeds that of adults. In discussing 4 different basal metabolism standards for children, Lewis, Duval and Iliff remark: "The closer any child comes to the mean values for height, weight and surface area of the group with which the standards were established, the less marked will be the discrepancy by the different methods of reference" (12). To emphasize their point they present the deviations of three 8-year-old boys from each of 4 standards. Three of the standards are essentially curvilinear regressions, of basal metabolism on surface area, weight and height, irrespective of age. The fourth is a per-surface area standard covering this single year of age. One boy is of average size and for him the standards agree well. One is small and the ratio standard places him about 14 per cent above the regression standards' estimates; the other is large and the ratio standard places him considerably below the regression standards' estimates. This is precisely the situation depicted in figure 1 of this paper, and the explanation is presumably similar. Probably this is also the explanation of the same authors' finding (13) that over the whole 2- to 12-year age range, the results of other workers average some 7 per cent for boys and 4 per cent for girls above theirs when the per-surface area standards are used, but are practically identical by the regression standards. These authors' children were somewhat larger than most of the others in the literature. They themselves remark in an earlier study that the per-surface area standard produces these positive deviations only in the case of children smaller than theirs (14): their claim that body build affects oxygen consumption needs careful examination by other methods than this before it can be accepted.

The same thing applies to many of the comparisons of basal metabolism between groups, racial and other, where mean differences of a few per cent may be reckoned significant; differences attributable to size must first be allowed for.

Oxygen Consumption and Body Build

The next example concerns this use of ratios in comparisons between groups. Seltzer has reported measurements of oxygen consumption at rest and during moderate and severe exercise for young men who were also measured anthropometrically (15). Oxygen consumption was reported as per-weight or per-surface area, and body measurements chiefly as indices. Considering the resting figures first, Seltzer divides his 34 subjects into two groups, one containing all those below the mean for the measurement or anthropological index in question, the other all those above it. He then compares the O_2/wt.

consumed by each group and considers whether the two O_2/wt. figures differ significantly. The first anthropological index taken is wt/stature, and it is shown that those subjects with a high wt/stature have significantly lower O_2/wt. consumptions than those with a low wt/stature. What effect is to be expected, however, from the spurious correlation involved?

We have seen above that a correlation between O_2/wt. and wt. will always exist (*equations E1* and *E2*) unless the condition $\frac{v_{wt.}}{v_{O_2}} = v_{wt.O_2}$ is satisfied. If $\frac{v_{wt.}}{v_{O_2}} > r$, the correlation between $\frac{O_2}{wt.}$ and wt. is negative, and if $\frac{v_{wt.}}{v_{O_2}} < r$, the correlation is positive. Taking an average value for v_{O_2} for Seltzer's data, we have a $\frac{v_{wt.}}{v_{O_2}}$ in this case of 1.8, far greater than r, which is 0.41. A large negative correlation therefore exists between $\frac{O_2}{wt.}$ and wt. Thus as the index $\frac{wt.}{stature}$ increases, $\frac{O_2}{wt.}$ must be expected to decrease purely as a result of the method used for presenting the data. The same is true for all anthropological indices which correlate positively with weight. Seltzer shows that this occurs for several indices, but his conclusion that more linear people have higher oxygen consumptions than stocky people is not justified by this data. Similar calculations, with similar results, can be made for the oxygen consumptions during exercise.

This is not to say, of course, that linear people do not in fact have higher oxygen consumptions. Such may well be the case, but other methods, of partial correlation or covariance analysis, are needed to demonstrate it. As a matter of a fact, there are two indices, span/stature and leg length/stature which remain significantly associated with oxygen consumption at rest when spurious relation is removed. It seems that men with short limbs and long trunks have higher oxygen consumptions relative to their surface area than do those with the opposite build.

Plasma Volume

The next example concerns the construction of standards and the choice between a per-weight and per-surface area standard for plasma volume. Gregerson has recommended that the per-weight standard be used for this measurement (16). Is this the best ratio standard available, and how great is the bias its use entails? These questions can be answered from the raw data on height, weight, surface area and plasma volume for 41 normal men given by Gibson and Evans (17). From this data the coefficients of variation of these variables can be calculated to be: height 4.9, weight 14.2, surface area 10.4 and plasma volume 15.8. The correlation coefficients are: plasma volume and height .72, weight .68, surface area .74. Does per-height, per-weight or per-

surface area standard most nearly coincide with its equivalent regression standard?

The $\frac{v_x}{v_y}$ for height is $\frac{4.9}{15.8} = .31$ and r_{xy} for height is .72, a figure very considerably different. *Equation H* gives the correlation between $\frac{\text{plasma volume}}{\text{height}}$ and height to be as much as +.51. For weight, $\frac{v_x}{v_y}$ is .90, and r_{xy} .68; there is still considerable discrepancy between these 2 figures, and the correlation of $\frac{\text{plasma volume}}{\text{weight}}$ and weight is −.29. (This can be seen illustrated in Gibson and Evans' fig. 5*B*). For surface area $\frac{v_x}{v_y}$ is .66 and r_{xy} .74. The agreement is much better, and the correlation of $\frac{\text{plasma volume}}{\text{surface area}}$ and surface area only +.12. Clearly the per-surface area is the best of these ratio standards, and the bias its use entails is of the same order of magnitude as that present in the basal metabolism standards. The plasma volume data of Mather, Bowler, Crooke and Morris, on 53 normal men (18) gave rise to almost identical figures, and thus to the same conclusion.

There are really two criteria by which to judge the efficiency of ratio standards. One is the closeness with which $\frac{v_x}{v_y}$ approaches r, and the second is the amount of variance of the dependent variable that is accounted for by the independent variable. This is given by the square of the coefficient of correlation between the variables. In our plasma volume example, surface area accounts for $.73^2 = 55$ per cent of the variance of plasma volume, and weight accounts for $.72^2 = 52$ per cent. Again the advantage lies with surface area, but very slightly, and if this was the only consideration, the claims of the per-weight standard, as Gregerson says, would be strong.

Glomerular Filtration Rate and Renal Plasma Flow

A last example may be taken from Houcks' recent study of renal plasma flow and filtration rates in dogs (19). Both these renal functions were calculated per-weight and per-surface area; surface area being calculated either from weight alone or from weight and length combined. No choice is made between the two, yet a very strong reason indeed exists for perferring the per-weight figures. The coefficient of variation of filtration rate was 33.7, of effective renal plasma flow 36.2, of weight 28.2 and of surface area 19.6 (for 75 resting female dogs). $\frac{v_x}{v_y}$ for filtration rate and surface area is .58 and their r is .75,

giving a correlation of $\frac{\text{filtration rate}}{\text{surface area}}$ and surface area of +.28. The per-weight ratio does much better: $\frac{v_x}{v_y} = .84$, $r = .80$, correlation $\frac{\text{filtration rate}}{\text{weight}}$ and weight −.06. For effective renal plasma flow it is the same, with surface area $\frac{v_x}{v_y} = .54$ and $r = .71$ with a correlation of $\frac{\text{plasma flow}}{\text{surface area}}$ and surface area = +.24; for weight, $\frac{v_x}{v_y} = .78$, $r = .80$, correlation $\frac{\text{plasma flow}}{\text{weight}}$ and weight −.03. By the second criterion weight is the better too: it accounts for more of the variance of each renal function than does surface area, as can be seen from the correlation coefficients.

This last example serves finally to recall our attention to the spurious correlation between indices. The author gives the correlation coefficients of $\frac{\text{filtration rate}}{\text{weight}}$ and $\frac{\text{plasma flow}}{\text{weight}}$ as .73; and between $\frac{\text{filtration rate}}{\text{surface area}}$ and $\frac{\text{plasma flow}}{\text{surface area}}$ as .79. He remarks these figures are relatively high, whichever one is taken, and there is a straight-forward physiological implication of such a fact. But part of this correlation is spurious, and to the detriment of his implied thesis, for the actual straightforward correlation between filtration rate and plasma flow for the data is .90. The agreement has been unnecessarily lowered by the use of the indices.

DISCUSSION

There remain two points to be discussed. In considering desirable standards or ways of reporting data it is often implied or explicitly stated that the best ratio standard is that which produces the smallest coefficient of variation of the data, the ratio which gives the least spread. The idea is a widespread one, and I have failed to trace its origin since recent authors take its correctness for granted, without need of a supporting reference. It rests to some extent on the belief that "the fact that the coefficient of variation of the data so calculated (renal functions as per-surface area) has the small magnitude of 13.1 per cent indicates a high degree of correlation (between the renal functions and surface area)" (20).

This statement is not strictly justified. The coefficient of variation of an index, variables ½, is

$$\frac{100\sqrt{v_1^2 - 2r_{12}v_1v_2 + v_2^2}}{1 - r_{12}v_1v_2 + v_2^2} \qquad (J)$$

Thus while it is true that the larger r is the lower is the coefficient of variation of the index, v_1 and v_2 play a larger part than does r. Even when $v_1 = v_2$,

$$v_{\text{index}} = \frac{100v_1\sqrt{2(1-r)}}{1+v_1^2(1-r)} \qquad (K)$$

and thus depends largely on the value of v_1.

There is only one circumstance in which this minimizing of the coefficient of variation of the ratio could actually produce the best standards. That would be if it made them coincide with the regression standard, in other words if minimizing the expression J reduced to the condition $\frac{v_1}{v_2} = r_{12}$. This it does not in fact do; the minimal J is actually secured by the rather more complicated condition

$$r_{12} = \frac{1}{2}\left(\frac{v_1}{v_2} + \frac{v_2}{v_1}\right)$$

Lastly, the relation between linear regression standards and standards of the form per-weight$^\alpha$ should be mentioned. The power standards, recently reviewed in the case of oxygen consumption by Kleiber (21), are more similar to the regression standards than to the ordinary ratio ones, despite first appearances. The reason for this is that the value of α is obtained by fitting a regression line to the logs of the variables. Thus the investigator relating oxygen consumption and body weight plots the log. of oxygen against the log. of weight and fits a regression line to the resulting scatter diagram. The equation of this regression line is

$$\log. O_2 = \alpha \log. \text{wt.} + \beta \qquad (L)$$

and this is equivalent to

$$O_2 = \beta' \text{ wt.}^\alpha. \qquad (M)$$

Is then the power standard as valid statisticallv as the regression standard and can the two be used replaceably?

The answer to the second of these questions is unequivocally no: and to the first, it depends on a particular circumstance, the nature of which does not seem to be widely realised amongst biologists. It has recently been discussed with masterly clarity by Sholl (22). The point is a simple one. When we fit a regression line to 2 sets of variables, we choose the line about which the sums of squares of deviations are a minimum. We do this because it follows from the method of maximum likelihood, a method for finding so-called efficient statistics which have great advantages over inefficient statistics (of which the ratio standard is an example). But the method of maximum likelihood only leads to this least-squares solution if for a given value of x, the independent

variable, the values of y, the dependent variable, are normally distributed. This is the thing that, as Sholl points out, is often overlooked. Now if we plot the logs. of x and y and fit by least squares a line to this graph, we are tacitly assuming that the logs. of y are normally distributed, not the raw values of y. It is not the case that if y is normally distributed log. y is also normally distributed; on the contrary. But in the usual method of constructing a power standard, α is obtained by *equation L*, which produces the best value for α if, and only if log. y is normally distributed and y itself is skewed. Where this is indeed the case, the power standard is the appropriate standard, and more valid than the linear regression standard. But where it is *not* the case, the power standard obtained this way is erroneous. Sholl has shown that a valid figure for α in *equation M can* be obtained in cases where y is normally distributed, but that it differs (often very considerably) from that produced by the method we have discussed involving *equation L*.

The upshot of this is that the power standard as usually calculated is only valid when there are sound statistical reasons for saying that the logarithms of the dependent variable, such as cardiac output, are normally distributed whereas the raw values of the dependent variable are significantly skewed. When this is not so, the regression standard is the standard which should be used. If, on biological grounds, it is felt that a standard of the form $O_2 = k\,wt.^{\alpha}$ is desirable, with α expressing active mass, then, if the variable O_2 is not significantly skewed, α must be found by Sholl's methods.

SUMMARY

The present standards which express physiological functions such as oxygen consumption and cardiac output as per-weight or per-surface area are shown to be theoretically fallacious and in practice (except in a special case) misleading. The fallacy involved in their application may be considered a special example of the spurious correlation between indices. Examples are cited of the undesirable practical effects of using such standards; the examples involve cardiac output, oxygen consumption and plasma volume in man, and glomerular filtration rate and renal plasma flow in the dog. The assumption that the best ratio standard is the one which minimizes the spread of the data concerned is criticized. The conditions are examined under which the power standard (e.g. $O_2 = wt.^{\alpha}$), as usually obtained, is valid; and the more common conditions where it is invalid unless α is obtained, by Sholl's method.

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Action of Caffeine and Aminophylline as Respiratory Stimulants in Man

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ALTHOUGH THE TWO XANTHINE derivatives, caffeine and aminophylline, have been used for many years as respiratory stimulants the mechanism of their action has never been clearly shown. The mechanism of action has been assumed to be that of increasing the sensitivity of the respiratory center to carbon dioxide. LeMessurier (1) studied the effect of caffeine on the respiration of dogs before and after extirpating the carotid sinuses and sectioning the vagi. His experiments were quite definite in demonstrating that the respiratory action of caffeine is mainly, if not entirely, a central action. As this direct approach is not possible in studying the respiratory action of these drugs in the human, indirect approaches to the problem must be considered. The use of the respiratory stimulating effect of carbon dioxide as a functional test would seem to be a logical approach to this problem. This approach is not an original one. Cushney (2) showed in 1913 that the increase in respiratory rate to carbon dioxide was greater after caffeine than before. Grabfield and Means (3) employed the reaction of respiration to increasing amounts of carbon dioxide in the inspired air as a criterion for judging the sensitivity of the respiratory center. Grabfield and Means concluded that as a result of taking various doses of caffeine by mouth there is no observable effect on the mechanism whereby increasing amounts of carbon dioxide increase ventilation. The validity of their conclusions, as well as those of many other early workers in this field, would seem open to question since they used the so called 'closed circuit' method of studying the effect of caffeine on the response of respiration to increasing amounts of carbon dioxide. In this method the subject rebreathes his own expired air and thus produces the carbon dioxide which serves as a stimulus to respiration. By this method the carbon dioxide content of the inspired air is constantly changing. Padget (4) showed that the maximum increase in respiration, when air containing an increased concentration of carbon dioxide is breathed, occurs only after the experiment has continued for some time. Thus a subject breathing a gas mixture containing 5 per cent carbon dioxide does not reach his maximum ventilation minute volume until after six or seven minutes. The subjects of Grabfield and Means were not exposed to any one concentration of carbon dioxide long enough to obtain a

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maximum response in ventilation volume to that concentration of carbon dioxide. In order to avoid this discrepancy, gases containing fixed and known concentrations of carbon dioxide were used in the present study.

If we could assume that carbon dioxide acts directly and solely on the respiratory center, then we could assume that any effect on the response of respiration to carbon dioxide by a drug must be due to its action on the center as a result of increasing or decreasing the sensitivity to carbon dioxide. This line of reasoning would have been acceptable before the work of Cordier and Heymens (5). As a result of their work the part played by the aortic and carotid chemoreceptors in response of respiration to carbon dioxide was first shown. However, Gemmill and Reeves (6) and Schmidt (7) have shown that with the concentrations of carbon dioxide used in this study, the chemoreceptors play no part in the response of respiration. Consequently the use of carbon dioxide as a functional test of respiratory center activity remains a sound approach to the problem.

The present study was undertaken to determine whether or not the action of caffeine and aminophylline on respiration is that of altering the sensitivity of the respiratory center to carbon dioxide.

METHODS

The apparatus consisted of a 500-liter chain compensated spirometer and a similar 100-liter spirometer. Flutter valves were arranged in the system connecting the two spirometers so that the subject inspired a known gas mixture from the large spirometer and expired into the small spirometer. The valves of the spirometers were so arranged that the patient could be switched from atmospheric air to the gas mixture without disturbing the patient, and similarly the expired air could be switched from the spirometer out into the room. The latter made possible the emptying of the small spirometer when this became necessary. This procedure required less than one minute, and the next volume measurement was begun at the beginning of the next minute. In graphing the resulting data this was taken into consideration. The usual rubber mouth piece and nose clip were used. The gases used were 3 and 5 per cent carbon dioxide in oxygen. Cylinders of the prepared compressed gas mixtures were used. The concentration of carbon dioxide was checked in the Haldane and Henderson-Haldane gas analysers. In each experiment the gas mixture was allowed to stand in the large spirometer for at least 30 minutes. Although observing the change in respiratory minute volume was the main interest of the work, electrocardiographic and pneumographic recordings were made in each phase of the experiment.

The subjects for the experiments with caffeine were 6 normal white males varying in age from 20 to 32 years. All of the subjects except *no. 1* were coffee drinkers.

The experiments were conducted in the early afternoon. No attempt was made to have the subject in the basal condition. The subject came to the laboratory without any previous preparation other than abstaining from caffeine-containing beverages at the noon meal on the day of the experiment. The subject usually arrived at the laboratory about 2 P. M. and rested on the metabolism cot for 15 to 30 minutes. Following this the mouth piece was inserted and the nose clip was adjusted. The subject was then allowed to breathe atmospheric air until the volume remained uniform for at least 4 minutes. With the aid of a stop watch minute readings were recorded from a meter stick attached to the small spirometer. Electrocardiographic and pneumographic tracings were made while the patient was breathing atmospheric air as well as in the other phases of the experiment after the minute readings became uniform. As soon as 4 uniform readings were obtained on atmospheric air, the valve was switched so that the subject breathed 3 per cent carbon dioxide in oxygen from the large spirometer. Minute readings were taken as before until these became uniform. In general the lag period corresponded with that reported by Padget (4). The mouth piece and nose clip were then removed and 0.25 grams of caffeine and sodium benzoate were given subcutaneously. The subject then rested on the cot for 30 minutes. At the end of this time the same procedure was repeated. In this way data was obtained under 4 different conditions, namely, breathing atmospheric air, breathing 3 per cent carbon dioxide in oxygen, breathing atmospheric air after caffeine, and breathing 3 per cent carbon dioxide after caffeine. On the following day the same procedure was repeated using 5 per cent carbon dioxide in oxygen. In computing results the differences between successive readings of the meter stick were reduced to minute volumes by using a known factor. Respiratory and cardiac rates were obtained from the electrocardiographic and pneumographic records.

In studying the effect of aminophylline four white males and one white female were used as subjects. The same procedure and conditions were used as in the previous series; 0.25 gm. of aminophylline was given subcutaneously.

RESULTS

The results of the experiments are shown by table and diagram. The ventilation minute volumes appearing in tables 1 and 2 were obtained by averaging figures obtained after the volumes had become uniform. The percentages of increase in ventilation minute volumes are based on volumes while the subject was breathing atmospheric air. The average per cent increase is based on the average of all the minute volumes on atmospheric air in each series.

Data in table 1 show clearly that in every case the ventilation minute volume was greater when the subject was breathing carbon dioxide after caf-

feine than before the administration of caffeine. The effect of caffeine on the ventilation minute volume when atmospheric air was being breathed was variable. In one experiment there was an increase of 20.7 per cent while in another there was a decrease of 18.1 per cent. It is of interest that on the

TABLE 1. EFFECT OF CAFFEINE ON VENTILATION MINUTE VOLUMES, CARDIAC AND RESPIRATORY RATES WHEN BREATHING ATMOSPHERIC AIR, 3% CO_2 AND 5% CO_2

	SUBJECT						% INCREASE
	1	2	3	4	5	6	
	Ventilation minute volumes, cc.						
Air	6159	7599	10,618	7766	6454	8277	
3% CO_2	9868	14,193	21,692	13,375	11,738	16,770	90.3
Air + caffeine	6561	8392	12,640	6360	6722	8469	6.2
3% CO_2 + caffeine	11,448	16,242	24,490	13,990	12,537	19,790	113
Air	6528	7593	9574	7264	6344	8302	
5% CO_2	20,915	24,079	30,824	19,205	19,130	36,042	225
Air + caffeine	5910	7900	8891	7431	6398	9412	−0.6
5% CO_2 + caffeine	28,253	27,128	36,500	21,004	21,300	39,936	277
	Cardiac rate/min.						
Air	66	84	72	96	66		
3% CO_2	60	84	78	90	66		−1.4
Air + caffeine	54	72	66				−13.5
3% CO_2 + caffeine	60	78	66	84	66		−7.4
Air	54	78	72	90	78		
5% CO_2	60	78	78	84	78		2.5
Air + caffeine		66	63	78	72		−12.2
5% CO_2 + caffeine	60	78	78	72	84		1.4
	Respiratory rate/min.						
Air	14	15	12	12		9	
3% CO_2	15	19	15	16		11	22.8
Air + caffeine	17	17	14	11		9	8.6
3% CO_2 + caffeine	18	19	16	13		11	23.8
Air	15	15	14	9	9	12	
5% CO_2	20	19	20	11	14	14	32.8
Air + caffeine	14	19	15	11	11	12	11.9
5% CO_2 + caffeine	23	21	23	12	14	17	48.0

following day opposite results were obtained in each of these cases. The average percentage increases of the 6 subjects are also shown in table 1. These reveal that when the subjects were breathing atmospheric air there was an increase in ventilation volume of 6.2 per cent after caffeine in the first 6 experiments, whereas there was a decrease of 0.6 per cent in the last 6 experi-

ments. The overall average of the 12 experiments is an increase of 2.8 per cent which does not appear to be significant.

Contrary to the results of Grabfield and Means (3) the increase in ventilation minute volume when breathing carbon dioxide after the administration of caffeine was striking in every instance. The average increase when breathing 3 per cent carbon dioxide after caffeine was 23.0 per cent greater than that without caffeine. With 5 per cent carbon dioxide the increase was 51.7 per cent greater with caffeine than without caffeine. These relationships are shown clearly in figure 1.

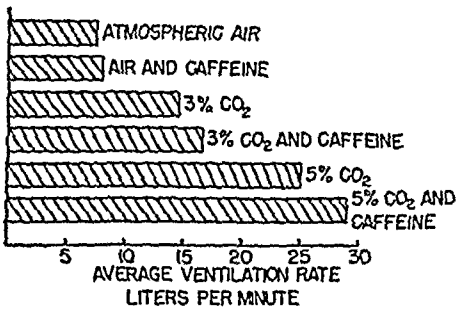

Fig. 1. AVERAGE EFFECT OF CAFFEINE on ventilation minute volumes of 6 subjects when breathing atmospheric air, 3% CO_2 and 5% CO_2.

Figure 2 shows a typical response to 3 and 5 per cent carbon dioxide in oxygen before and after caffeine. It illustrates the importance of the time element in reaching a maximum response in respiration when breathing air containing an increased percentage of carbon dioxide.

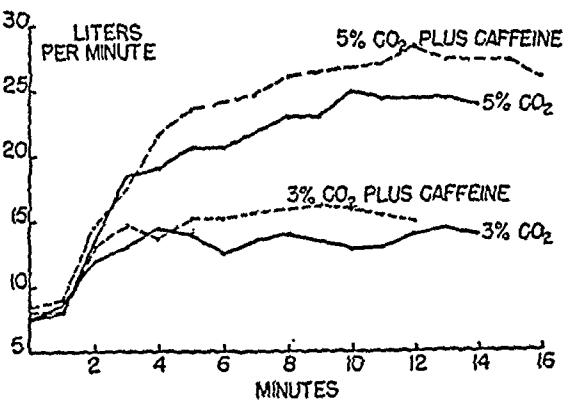

Fig. 2. TYPICAL RESPONSE OF RESPIRATION to 3% CO_2 and 5% CO_2 before and after administration of caffeine.

Cardiac and respiratory rates obtained from the caffeine series are recorded in table 1. These represent rates after a uniform volume of respiration had been reached. Carbon dioxide showed no consistent effect on cardiac rate. Caffeine caused a decrease in cardiac rate in each case in which cardiac rate was recorded while the patient was breathing atmospheric air. The latter is in agreement with the observations of Starr *et al.* (8). No significant electrocardiographic changes were observed.

In general, caffeine caused an increase in respiratory rate when the subject was breathing atmospheric air as well as when breathing carbon dioxide. However this did not occur in every case.

The reliability of the technic used in this study was tested on one of the subjects. Without the knowledge of the subject, normal saline was administered in place of the usual caffeine. The respiratory minute volumes of the control were even less after the injection than before with both atmospheric air and carbon dioxide.

TABLE 2. EFFECT OF AMINOPHYLLINE ON VENTILATION MINUTE VOLUMES, CARDIAC AND RESPIRATORY RATES WHEN BREATHING ATMOSPHERIC AIR, 3% CO_2 AND 5% CO_2

	SUBJECT					% INCREASE
	1	2	3	4	5	
	Ventilation minute volume, cc.					
Air	9625	8503	6936	7599	7450	
3% CO_2	15,399	18,434	12,553	12,921	17,920	89.2
Air + aminophylline	8493	9239	7154	7610	8440	0.3
3% CO_2 + aminophylline	16,670	18,344	12,370	14,015	19,810	99.0
Air	9195	8700	7275			
5% CO_2	23,566	31,490	18,860			202
Air + aminophylline	8599	10,190	6990			5.3
5% CO_2 + aminophylline	24,102	29,710	18,384			195
	Cardiac rate/min.					
Air	96	64	84	78	76	
3% CO_2	102	68	80	72	76	0.0
Air + aminophylline	90	60	84	72	72	−5.1
3% CO_2 + aminophylline	84	64	76	72	77	−5.7
Air	90	72	76			
5% CO_2	96	68	84			3.9
Air + aminophylline	84	60	76			−7.7
5% CO_2 + aminophylline	78	65	76			−7.7
	Respiratory rate/min.					
Air	21	10	11	11	9	
3% CO_2	23	9	12	11	15	15.0
Air + aminophylline	19	10	9	14	19	22.1
3% CO_2 + aminophylline	18	10	11	13	18	20.8
Air	17	12	11			
5% CO_2	20	20	12			31.1
Air + aminophylline	19	12	11			3.9
5% CO_2 + aminophylline	20	11	11			3.1

Following the subcutaneous injection of 0.25 gm. of aminophylline there was no significant increase in the average ventilation minute volumes either when the subject was breathing atmospheric air, 3 per cent or 5 per cent carbon dioxide as shown in table 2. The individual results were not consistent, some

showing an increase while others showed a decrease in ventilation minute volumes. This was in marked contrast to the consistent results obtained with caffeine.

Cardiac and respiratory rates obtained from the aminophylline series are recorded in table 2. Aminophylline caused a slight decrease in cardiac rate when the subjects were breathing atmospheric air as well as when they were breathing carbon dioxide. As in the caffeine series carbon dioxide showed no consistent effect on cardiac rate.

The results recorded in the last section of table 2 are inconsistent. However, the average shows an increase in respiratory rate following the administration of aminophylline when the subject was breathing atmospheric air. An increase in respiratory rate was observed after aminophylline when the subjects were breathing 3 per cent carbon dioxide and a decrease when breathing 5 per cent carbon dioxide. This latter inconsistency appears to be due to the hyperactive response of *subject no. 5*, who was the only female subject used in the series.

DISCUSSION

That the use of the respiratory stimulating effect of carbon dioxide as a functional test is a sound approach to this problem has already been discussed. If caffeine acts directly on the respiratory center as a specific stimulus, one would expect the effect to remain constant regardless of whether the patient is breathing atmospheric air, 3 per cent carbon dioxide, or 5 per cent carbon dioxide. This is certainly not the case in the present study. Whereas caffeine increased the ventilation volume only an insignificant 2.8 per cent with atmospheric air, the increase was 23.0 per cent with 3 per cent carbon dioxide and 51.7 per cent with 5 per cent carbon dioxide. Since carbon dioxide acts directly on the respiratory center, and since caffeine increases this action by 23.0 per cent in the case of 3 per cent carbon dioxide and 51.7 per cent in the case of 5 per cent carbon dioxide, then the action of caffeine must be that of rendering the respiratory center more sensitive to carbon dioxide.

It is most interesting that, although the two drugs used in the present study are closely related in chemical structure and both are effective in the treatment of Cheyne-Stokes respiration, the mechanism of their actions does not appear to be the same. From the present study it would seem that the effectiveness of caffeine in Cheyne-Stokes respiration is its ability to render the respiratory center more sensitive to carbon dioxide. Just how aminophylline renders its effects in the treatment of the condition must await further investigation. Apparently it is a mechanism different from that of caffeine.

The fact that the ventilation minute volume is much greater with both caffeine and carbon dioxide in oxygen than with carbon dioxide in oxygen alone

should be of practical importance in decreasing the recovery period of patients with carbon monoxide poisoning and in stimulating respiration in severe respiratory depression.

SUMMARY

The effect on ventilation minute volumes, cardiac and respiratory rates of 0.25 gm. of caffeine and sodium benzoate administered subcutaneously was observed in 6 subjects while breathing atmospheric air, 3 and 5 per cent carbon dioxide in oxygen. This same effect was observed in 5 subjects following the subcutaneous administration of 0.25 grams of aminophylline. Caffeine and aminophylline showed a variable effect on ventilation minute volume with a slight average increase when the subject was breathing atmospheric air. The ventilation minute volume was strikingly increased in every case after caffeine when the subject was breathing either 3 or 5 per cent carbon dioxide in oxygen. After aminophylline the effect was very inconsistent and the average effect was not significant. Cardiac rate showed no consistent response to carbon dioxide. Both caffeine and aminophylline caused slowing of the cardiac rate. Neither carbon dioxide, caffeine, nor the combination caused any significant change in the electrocardiogram. No significant change in electrocardiogram was observed following the administration of aminophylline. In general caffeine and aminophylline caused an increase in respiratory rate. Some practical applications of the observations of this study are mentioned.

It is concluded from this study that caffeine acts on the respiratory center by increasing its sensitivity to carbon dioxide. The mechanism of the action of aminophylline in the dose used in this study does not appear to be similar to that of caffeine.

The author wishes to express his appreciation to Dr. C. L. Gemmill, for suggesting this problem and for his advice and criticism throughout the investigation. The author also wishes to thank the Division of Research Grants and Fellowships of the National Institute of Health, U. S. Public Health Service, for financial support in part for this work.

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Pulmonary 'Capillary' Pressure in Man[1]

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UNTIL THE DEVELOPMENT of the technique of venous catheterization by Cournand and Ranges (1), no method was readily available for studying pulmonary circulatory dynamics in man. The introduction of this technique has permitted the elucidation of many problems of the lesser circulation in health and disease, until at present the pressures in the right side of the heart and pulmonary artery are common knowledge. Using this technique, a method has been developed by which the capillary pressure of the human lung may be estimated.

In a previous communication (2), the technique of estimating pulmonary 'capillary' pressure in the lungs of animals was reported. In this paper the method as applied to the human lung is described. In subsequent communications the results obtained in patients with heart and pulmonary disease under conditions of rest and exercise will be reported.

METHODS

Thirteen patients were selected for study who had normal cardiovascular systems as far as could be judged from history, physical examination, X-ray, and electrocardiogram. The majority had primary syphilis and were studied at least 48 hours after the institution of penicillin therapy. Ten were males, three were females, and their ages varied from 18 to 40 years. The subjects were studied in a resting state under fasting conditions. Venous catheterization was carried out under fluoroscopic guidance, the catheter being introduced into a distal branch of the pulmonary artery so as to occlude it. The size of the vessel occluded varied between about 2 and 3 mm. depending on the catheter size. Measurements of the pressure existing distal to the occluding catheter were recorded through the hole in the tip of the catheter with a column of saline and with a Hamilton manometer (3). The pressure recorded in this fashion in this occluded vessel will be referred to as the pulmonary 'capillary' pressure for reasons that will be discussed later. The catheter was then withdrawn so as to lie free in the pulmonary artery and pressures were again recorded.

In 7 individuals with arterial oxygen unsaturation due to a right-to-left shunt within the heart or to pulmonary or hepatic disease (see table 2), blood samples were withdrawn under oil from a systemic artery and through a catheter occluding the lumen of a branch of the pulmonary artery. These bloods were analyzed by the method of Van Slyke and Neill (4) for oxygen content, capacity, and saturation.

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In 2 patients with atrial septal defect, venous catheterization was carried out as described elsewhere (5, 6). In each case the catheter was introduced through the defect into the left auricle and out into a pulmonary vein so as to occlude it. After recording the pressure, the catheter was withdrawn to the right auricle and introduced into the right ventricle and pulmonary artery where it was wedged into a distal branch where pressures were again recorded.

The zero point for all pressures was taken 10 cm. anterior to the spine with the subject in the supine position. The antero-posterior diameter of the chest was recorded for the convenience of those using other zero points of reference. Mean pressures were obtained with the saline manometer and by planimetric integration of the Hamilton pressure tracings.

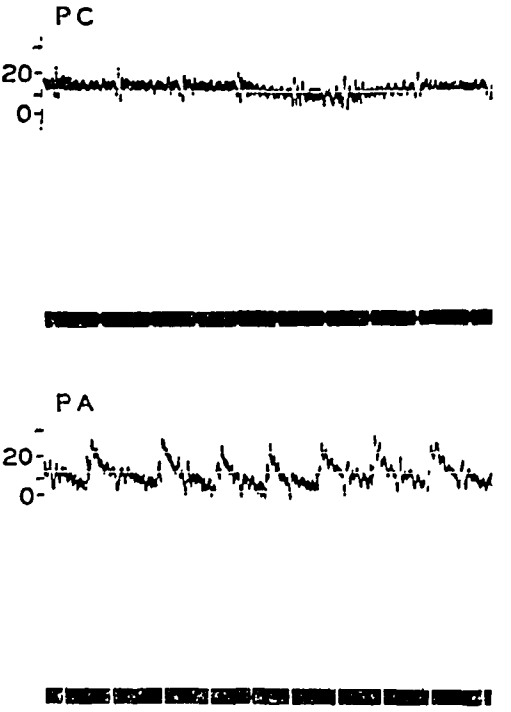

Fig. 1. PRESSURE TRACINGS FROM THE PULMONARY 'CAPILLARIES' (PC) and pulmonary artery (PA) in a normal individual. Note the respiratory variation of pressure and the lack of definite pulsations in the 'capillary' curve. The lower tracing shows the typical pulsatile contour of the pressure in the pulmonary artery. In each tracing, there are numerous artefacts due to motion of the catheter within the heart.

RESULTS

In 13 normal individuals, the contour of the pressure curves obtained through the catheter occluding the pulmonary artery was distinctly different from that obtained when it lay free in the pulmonary artery. As can be seen from figure 1, no definite pulse wave was visible but there was frequently a considerable respiratory variation in the pressure, the pressure being lower on inspiration than in expiration by an average of 8 mm. Hg (table 1). In these 13 patients, the mean pressures at rest averaged 10 mm. Hg with a variation from 7 to 15 (table 1). The pulmonary artery pressures varied between 19 and 30 mm. Hg systolic and 6 and 12 diastolic with an average pressure of 24/10.

TABLE 1. PULMONARY ARTERY AND PULMONARY 'CAPILLARY' PRESSURES, PRESSURE GRADIENT, AND PULMONARY VASCULAR RESISTANCE IN 13 NORMAL INDIVIDUALS

CASE NO.	PATIENT	A-P DIAMETER OF CHEST	PULMONARY ARTERY PRESSURE, MM. HG				PULMONARY 'CAPILLARY' PRESSURE, MM. HG				PRESSURE GRADIENT BETWEEN PULMONARY ARTERY AND PULMONARY 'CAPILLARIES'
			Systolic	Diastolic	Mean		Inspiration	Expiration	Mean		
					Hamilton	Saline			Hamilton	Saline	
		cm.									*mm. Hg*
1	*R. A.*	19.0	23	10	18	17	6	13	10		8
2	*E. B.*	21.0	28	12	21		2	22	15	11	6
3	*A. C.*	15.5	23	10	17	16	8	16	13	11	4
4	*M. C.*		25	12	17		5	10	8		9
5	*J. D.*	21.0	25	12	17	19	8	10	9	12	8
6	*E. F.*	20.0	26	10	15		2	12	7		8
7	*N. F.*	21.0	30	9	18		5	14	11		7
8	*H. H.*	17.5	19	7	11	17	3	10	7	12	4
9	*U. M.*	18.0	23	6	13	16	5	12	9	11	4
10	*J. M.*		25	10	16	15	10	14	13	12	3
11	*M. N.*	15.0	24	10	17	17	8	16	12		3
12	*W. P.*	19.0	22	6	14		6	12	9	10	5
13	*F. R.*		23	10	13		3	10	7		6
Average.....			24	10	16		5	13	10		6

TABLE 2. OXYGEN SATURATION OF PULMONARY 'CAPILLARY' BLOOD IN PATIENTS WITH SYSTEMIC ARTERIAL OXYGEN UNSATURATION

CASE NO.	PATIENT	DIAGNOSIS	SYSTEMIC ARTERY			PULMONARY END ARTERY		
			O_2 content	O_2 capacity	O_2 saturation	O_2 content	O_2 capacity	O_2 saturation
Arterial oxygen unsaturation resulting from a right-to-left cardiac shunt								
			cc/l.	*cc/l.*	*per cent*	*cc/l.*	*cc/l.*	*per cent*
1	*A. D.*	Tetralogy of Fallot	171	257	66	234	238	98
2	*V. R.*	Tetralogy of Fallot	233	285	82	276	285	97
3	*J. C.*	Tetralogy of Fallot	151	163	93	165	166	99
Arterial oxygen unsaturation of pulmonary or other origin								
4	*M. G.*	Mitral stenosis Pulmonary congestion	169	188	90	177	180	98
5	*M. D.*	Aortic stenosis, anemia Pulmonary congestion	101	113	89	110	113	97
6	*S. A.*	Hepatic failure	203	224	91	202	204	99
7	*W. M.*	Emphysema	167	207	81	195	200	98

The mean pulmonary artery pressure as determined by planimetric integration of the pressure curves was 16 mm. Hg at rest with variations between 11 and 21. The gradient of pressure between the pulmonary artery and the pulmonary 'capillaries' varied between 3 and 9 mm. Hg with an average of 6.

Blood samples withdrawn through a venous catheter occluding a branch of the pulmonary artery in patients with arterial oxygen unsaturation from various causes were found to be fully saturated with oxygen (table 2).

In 2 patients with atrial septal defect in whom pressures were recorded through the catheter first wedged into the pulmonary vein and then into the pulmonary artery, the pressures recorded on the two sides of the pulmonary capillary bed are shown in table 3, and it will be seen that the values were identical.

TABLE 3. PRESSURES IN PULMONARY ARTERY, IN OCCLUDED PULMONARY ARTERY, AND IN OCCLUDED PULMONARY VEIN OF PATIENTS WITH ATRIAL SEPTAL DEFECT

CASE NO.	PATIENT	PULMONARY ARTERY PRESSURE, MM. HG			PULMONARY END ARTERY MEAN PRESSURE, MM. HG		PULMONARY END VEIN MEAN PRESSURE, MM. HG	
		Systolic	Diastolic	Mean	Hamilton Manometer	Saline Manometer	Hamilton Manometer	Saline Manometer
1	*S. W.*	41	21	30	10	11	11	11
2	*V. E.*	29	9	20	11	7	11	7

DISCUSSION

In a previous communication (2) evidence was presented that in dogs the pressure beyond the point of occlusion of a small branch of the pulmonary artery was about 2 mm. Hg less, and that the pressure measured on the capillary side of a small occluded pulmonary vein was about 2 mm. Hg more than the true pulmonary capillary pressure. This relationship held over a wide range of capillary pressure. The validity of this method of determining the pressure in the pulmonary capillaries is based on the following evidence (fig. 2).

1) The pulmonary arteries ramify and finally end in the capillaries, there being no pre-capillary anastomoses with adjacent pulmonary arteries (7, 8). This is supported by the physiological observation that in normal individuals blood withdrawn through a catheter occluding the lumen of a branch of the pulmonary artery is fully saturated with oxygen (9).

2) There is normally an anastomosis between the bronchial arterial and pulmonary arterial circulations in the capillary bed of the lung (7, 8). No evidence for the existence of any significant pre-capillary anastomoses has been found because, as shown in table 2, in individuals with oxygen unsaturation of the systemic (and therefore bronchial) arterial blood, whether of shunt origin in heart or lung, full arterial oxygen saturation has been found in the blood samples withdrawn through a catheter occluding a branch of the pulmonary

artery. If there were any significant pre-capillary anastomoses of the bronchial arteries with the pulmonary arteries, the samples withdrawn through the catheter would have had some degree of oxygen unsaturation.

3) There are no valves in the pulmonary artery, vein, or capillaries anatomically (7, 10) or physiologically (2), so that there is free retrograde flow, cross-flow, and transmission of pressure from the pulmonary capillaries to the catheter wedged into the pulmonary artery.

4) The capillary bed of the lung contains such a rich network of vessels that blood may actually be aspirated back from the capillaries through the catheter occluding the pulmonary artery (9).

In two patients with atrial septal defect, the identity of pressures recorded on the capillary side of an occluded pulmonary artery and vein further support the interpretation that these pressures are close approximations of the true

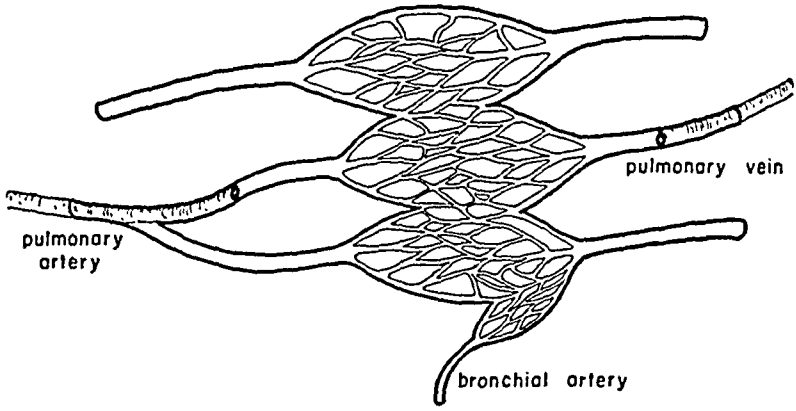

Fig. 2. DIAGRAM OF THE PULMONARY CAPILLARY CIRCULATION as applied to this study showing catheters wedged into the pulmonary artery and pulmonary vein. For a more detailed description and diagram of the pulmonary circulation, see Bruner and Schmidt (8).

pulmonary capillary pressure (see table 3). Any error on the arterial side will be in the direction of a lower reading than the true capillary pressure (2). In dogs, this amounts to only a few millimeters of mercury (2). For this reason, the term 'capillary' pressure is enclosed in quotation marks.

The average pulmonary 'capillary' pressure obtained in the manner described was 9 mm. Hg in 13 normal patients. The gradient of pressure between pulmonary artery and 'capillaries' averaged only 6 mm. Hg at rest.

SUMMARY

A venous catheter has been introduced into the pulmonary artery of man and wedged into a distal ramification so as to obstruct its lumen. Blood samples withdrawn through this catheter in individuals with systemic arterial oxygen unsaturation were fully saturated with oxygen, indicating the lack of any significant pre-capillary admixture of bronchial with pulmonary arterial

blood. Pressures recorded through the catheter in the position described have been found to be identical with those recorded through a catheter wedged into a pulmonary vein in two patients with atrial septal defects. It is therefore believed that both pressures are close approximations of the true pulmonary capillary pressure.

The pulmonary 'capillary' pressure was found to average 10 mm. Hg with a variation between 7 and 15 in 13 normal patients. The mean pulmonary artery pressure in these individuals averaged 16 mm. Hg with variations between 11 and 21. The gradient of pressure between pulmonary artery and pulmonary 'capillaries' varied between 3 and 9 mm. Hg with an average of 6.

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Electrokymographic Studies of Lung Field Pulsations with Exhalation against Pressure[1]

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LUNG FIELD PULSATIONS can be obtained by means of the electrokymograph (1) as has been previously reported (2). They are related in timing to the pulse waves obtained from the pulmonary artery. This can be verified by studying the time relationships of electrokymographic waves from the aorta and pulmonary artery, with those obtained from the lung fields in cases of marked ventricular asynchronism. The authors believe that lung field pulsations are related principally to the pulmonary circulation and further that they represent, for the most part, blood volume changes in the area under observation. It is believed, however, that at least 3 additional factors enter into the composition of these waves, namely pulsations of the bronchial arteries and veins, transmitted pulsations from the heart, and changes in density of the lung field due to alteration in aeration especially when expiration is attempted against resistance.

Accordingly electrokymograms were taken over the lung fields of normal subjects during forced expiration against a closed glottis (Valsalva's experiment). The systemic pulse (glycerin capsule over the radial artery) and the lung field pulse showed immediate reduction in amplitude which lasted for 3 to 5 seconds followed by a gradual increase in amplitude. Ten such experiments were done and it was noted that some distortion occurred in the first few pulses obtained from the lung fields and that no corresponding distortion occurred in the systemic pulse.

In as much as no corresponding distortion occurred in the systemic pulse in view of the reports by Fenn and Chadwick (3) as well as the curve published by Bard (4) of Bazett's unpublished experiment and since Westermark (5) reported that he could obtain pulmonary artery pressure by means of serial radiographs of the lungs while varying the intrabronchial pressure, it was decided to study the relation of the lung field pulse to measured resistances to exhalation.

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METHODS

Lung field pulsations were recorded by means of the electrokymograph directed over the third or fourth intercostal space anteriorly on the right side. This site was chosen fo two reasons: *1*) peripheral to the mid-clavicular line the lung field pulsations as recorded electrokymographically are less distinct; and *2*) it was felt that this represented the most lateral area with respect to the heart at which a minimum of transmitted waves from the heart would affect the electrokymogram. Pulsations were recorded under the following conditions: normal respiration and exhalation against known resistances by means of the apparatus described in figure 1. In order to identify and correlate the lung field pulsations indirectly with the pulmonary arterial pulse an electrokymogram of the pulmonary artery along

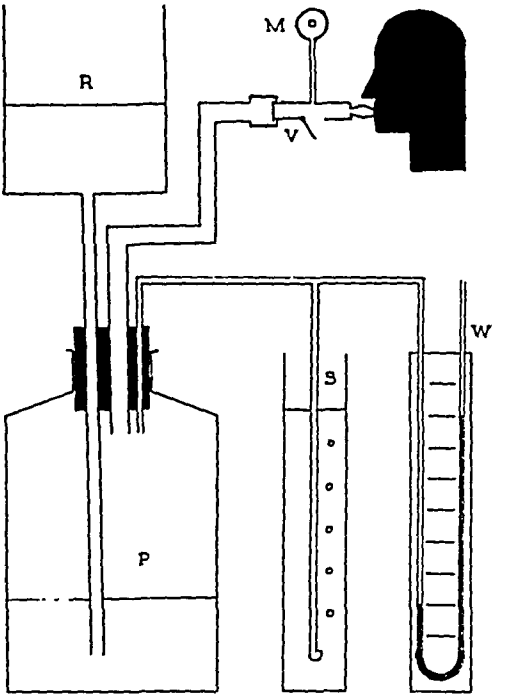

Fig. 1. SCHEMATIC SKETCH OF APPARATUS for obtaining exhalation against resistance. Patient inserts mouth piece of V in mouth: during normal respiration no interference occurs; when exhalation is against pressure the opening to the room air is closed. P is the pressure bottle into which water from the reservoir R is allowed to flow until a predetermined pressure is attained. The standpipe S and the water manometer W are used in fixing the pressure against which exhalation is to be attempted. M is the glass membrane manometer which registers the actual pressure against which exhalation was attempted.

the left border of the cardiac silhouette and also the radial artery sphygmogram (carotid pulse was not used because of the likelihood of stimulation of the carotid sinus reflex by the neck clamp usually used for obtaining the carotid pulse when exhalation was against pressure) were simultaneously recorded on photographic paper. The radial artery sphygmogram was then continuously recorded with the lung field pulsations. For purposes of determining the resistance against which the individual exhaled, a glass membrane manometer was placed in the system and its displacement was simultaneously recorded with the radial artery and lung field pulsations.

A series of experiments was done under various conditions before determining the method of applying resistance to exhalation. The method chosen is described in figure 1. The resistance was applied for approximately 10 to 20 seconds. Twenty-three experiments were done on 22 individuals using the technique described.

TABLE 1

	SEX AGE	RESISTANCE TO EXHALATION IN CM. H_2O	FINDINGS AND COMMENT
S. G.	M52	10, 15, 20, 25, 30	At pressures of 20 cm. and above, a significant decrease in the pulsations, first few pulses immediately after onset of pressure breathing were almost obliterated.
E. H.	F53	10, 20, 30, 40	At 30 cm., lung field pulsations disappeared.
W. H.	M23	10, 20, 30, 40	Two pulsations greatly depressed immediately after exhalation between 25 cm. and 30 cm.
M. P.	F33	Gradual increase from 0 cm. to 40 cm.	At approximately 30 cm., pulsations markedly depressed.
R. G.	M67	10, 20, 30, 40	At 30 cm., first few pulsations distorted in configuration and time relationship to radial sphygmogram changed.
E. J.	M34	10, 20, 30	At 30 cm., pulse waves disappeared at beginning of pressure exhalation.
R. K.	M26	20, 25, 30, 35, 40, 45	One pulse wave apparently missing at 45 cm.
J. P.	M26	20, 30, 40	One pulse wave missing at 20 cm.; pulse wave nondescriptive above 40 cm.
J. P.	M26	25, 30, 40, 45, 50	One pulse wave missing at 35 cm.; almost obliterated at 50 cm. and above.
R. L.	M23	20, 25, 30	Pulse waves diminished at 30 cm.
H. D.	M25	20, 25, 30, 35, 40	Pulse waves almost disappeared at 35 cm.
J. A.	M44	15, 20, 30	Definite decrease in pulsations at 30 cm.
J. T.	F69	20, 30	Questionable marked decrease of one pulsation at 30 cm.
E. A.	M30	25, 30	Marked decrease of pulsations at 25 cm. Syncope at 30 cm.
S. A.	M56	10, 20, 30	Pulse waves reduced and distorted at 30 cm.
E. S.	M37	25, 35	Marked reduction of pulse waves at 35 cm.
R. H.	M22	25, 30, 35, 40, 45, 50	Pulsations reduced in size at all pressures.
A. M.	M22	25, 32, 40, 50	First few pulse waves reduced in amplitude, and after onset of exhalation at all pressures.
E. R.	M18	20, 30, 40	No significant change in pulse waves.
R. O.	M22	10, 20, 30, 40	No significant change in pulse waves.
J. L.	M25	20, 30, 40	No significant change in pulse waves.
R. S.	F20	25, 32, 40, 45, 50	No significant change in pulse waves up to 50 cm. water. At 50 cm. questionable change of one pulse wave.
L. S.	M52	30, 40, 45	No significant change in pulse waves noted. Higher pressures were not done because patient could not tolerate any increase of resistance to pressure exhalation.

Eighteen of the individuals had no gross evidence of cardiac or pulmonary disease. *Subject 14* (E. A.) had an active minimal pulmonary tuberculosis; *subject 17* (R. H. had neurocirculatory asthenia; *subject 22* (R. S.) had chronic bronchitis of undetermined etiology as well as abnormal motion of the right ventricular wall as determined by the electrokymograph; *subject 23* (K. S.) had congenital heart disease of the Eisenmenger type.

RESULTS

The resistances to exhalation in centimeters of water as well as the results observed in the electrokymograms of the lung fields are recorded in table 1

Heart catheterization was performed on *subjects 1* (S. G.) and *23* (L. S.). The catheterization studies on *subject 1* (S. G.) showed the following mean pressures:

Superior vena cava	4 cm. H_2O
Right auricle	0
Right ventricle	10
Left pulmonary artery	13 to 16

The pressures on *subject 23* (L. S.) were as follows:

Superior vena cava	14 cm. H_2O
Right auricle	9 2
Right ventricle	60
Right pulmonary artery	60

Subjects 1 to *9* inclusive showed significant changes in the lung field pulsations occurring at or above rather definite pressures. Figure 2 shows an example of this group, it illustrates the lung field electrokymograms of *subject 1* (S. G.), one of the patients whose heart was catheterized

Subjects 10 to *18* inclusive had less pronounced changes occurring in the lung field pulsations but nevertheless showed some changes as indicated in table 1

Subjects 19 to *23* inclusive showed no significant change in the lung field pulsations at the pressures studied

DISCUSSION

It is apparent from the results obtained that changes in the lung field pulsation can occur when the resistance to exhalation is increased to pressures which approximate or exceed those noted in the right ventricle and in the pulmonary artery (6, 7) of normal individuals. The changes noted vary from definite diminutions in the height of the pulse wave to the near obliteration of one or more pulse waves immediately after pressure is increased

The full explanation of these changes in the lung field pulse is as yet not available, however, various authors (8-12) report that exhalation against pressure reduces the cardiac output. Humphreys *et al* (9) noted a rise in the venous pressure and the pulmonary artery pressure accompanied by a decrease in the pulse pressure of the pulmonary artery. They felt that the reduction in cardiac output was due to compression of the heart and its afferent vessels which interfered with filling, as well as compression of the pulmonary vessels, which interferes with emptying. Carr and Essex (12) apparently feel that the increased venous return is due to a cardiac tamponade effect produced by the

increased intrathoracic pressure. From the work of Gibbon *et al.* (13) obstruction of the pulmonary artery to the extent of 60 per cent of its cross-sectional area is necessary before a reduction in cardiac output is apparent. The suddenness of elevation of the intrathoracic pressure as carried out in these ex-

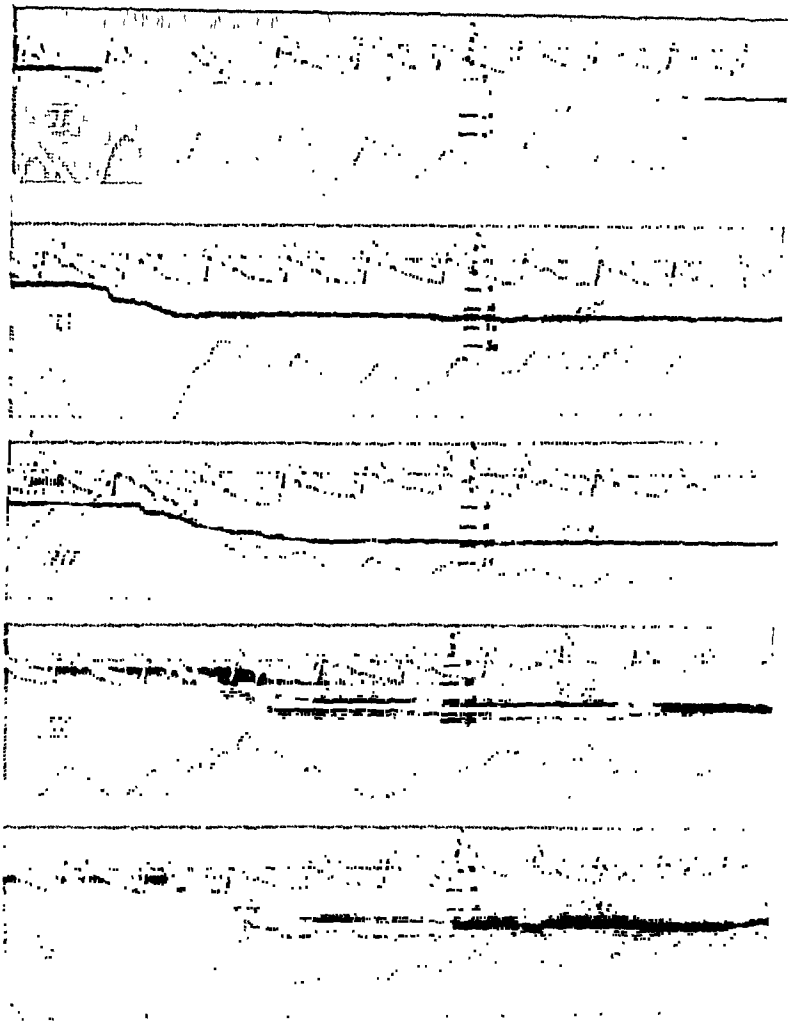

Fig. 2. LUNG FIELD ELECTROKYMOGRAMS FROM *subject 1* (S. G.). The pulse waves at the top are from the radial artery; the waves at the bottom are the lung field pulsations obtained by the electrokymograph; the black line is the registration of pressure by the glass membrane manometer. Initially the manometer describes zero pressure. The number with each curve indicates the pressure in centimeters of water against which exhalation actually occurred. In records I and II, *little* or *no* change occurs with the lung field pulse when the resistance to exhalation is 10 cm. and 15 cm. of water. In III the pulse waves are diminished. In IV and V the pulse waves are markedly diminished with near obliteration of the first few pulse waves.

periments, it might be conjectured, could produce an immediate obstruction to venous return and pulmonary outflow, thus causing a cardiac tamponade with an accompanying distorted or absent pulse wave. The immediate recovery of the wave to the undistorted form could then be explained on the basis that *1*) pulmonary artery pressure rises with the increased intrathoracic

pressure maintained at a relatively constant level thus overcoming the outflow obstruction and 2) venous return re-establishes itself on the basis noted by Meyer and Middleton (14) that venous pressure does not continue to rise if there is a 'leak' in the expiratory effort. The transiency of the near obliteration or distortion of the pulse wave from the lung field might be similar to the effects noted by Fenn and Chadwick (3) on the volume pulse of the finger during the first few seconds after pressure breathing begins.

In the group of patients showing no significant change, 2 individuals show evidence of disturbances of the cardio-respiratory mechanism (*subject 22* had a chronic bronchitis and an abnormal electrokymogram of the right ventricle and *subject 23* a congenital heart of the Eisenmenger type with a pulmonary artery tension of 60 cm. of water). It might be inferred that possibly the resistance to exhalation was far below that necessary to affect the pulmonary circulation. Should this be true then it would seem reasonable to assume that the principal mechanism operating to produce the decrease in volume pulse as well as the near obliteration or distortion of one or more of the first few pulse waves from the lung fields immediately after the inset of exhalation against resistance was the sudden compression of the pulmonary vessels as described by Humphreys *et al.* (9), with such temporary interference with venous return so that one or more cardiac cycles were necessary to increase pulmonary pressure sufficiently to overcome the compression.

The fact that lung field pulsations can be recorded and further that they can be affected by exhalation against resistance would seem to offer a fertile field for further exploration of tension relationships in the pulmonary circulation.

SUMMARY

Lung field pulsations can be recorded by means of the electrokymograph. Lung field pulsations were affected in contour and amplitude in 18 out of 23 experiments by exhalation against resistance. Whether a definite relationship exists between the blood pressure in the pulmonary circulation and the change in lung field pulse when exhalation is against resistance is suggested, but remains to be determined.

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Alveolar Gases in Rapid Decompression to High Altitudes

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PROMPTED BY THE DEVELOPMENT of pressure cabin aircraft during the last ten years a considerable number of studies in aviation medicine have been directed to the effects of rapid decompression. Thus far the main interest has been focused on the immediate mechanical effects of extreme and sudden reduction of the total barometric pressure on living organisms, such as expansion of internal body gases and the formation of gas bubbles in blood vessels, cerebrospinal fluid and tissues. Fortunately the physical dangers of rapid decompression have been substantiated only to a limited degree. Based on data available today it is safe to say that a drop in ambient pressure from one atmosphere to one-tenth of an atmosphere within fractions of a second may be injurious but not necessarily fatal to man provided there is no respiratory obstruction.

In view of the foregoing the immediate dangers of rapid decompression would result from a subsequent lack of oxygen rather than the mechanical effects per se. For this reason accurate knowledge of the special characteristics of hypoxia brought about by rapid decompression is urgently necessary for the development of measures to be taken for the survival and revival of airmen suddenly exposed to stratospheric pressures. The first step toward this end is the investigation of pulmonary gas exchange while breathing ambient air or oxygen, whichever the case may be, when the rapid decompression occurs. In estimating the physiological effects of altitude, breathing air or oxygen, equivalent degrees of hypoxia are to be expected whenever the alveolar oxygen pressures are identical. Convincing experimental evidence has also been gathered to demonstrate that physiologically equivalent altitudes may be calculated with considerable accuracy on the basis of tracheal oxygen pressures (1), and this procedure has been generally adopted in establishing standards for oxygen equipment.

Tracheal oxygen pressures (pO_{2trach}) are calculated from the ambient barometric pressure (B) allowing for a water vapor pressure of 47 mm. Hg at body temperature and the oxygen fraction in the inspired gas (F_{O2insp}) by the following equation:

$$pO_{2trach} = (B - 47)\, F_{O2insp} \qquad (1)$$

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In a strict sense the 'tracheal equation' as a means of estimating hypoxia is valid only under conditions in which the amount of carbon dioxide passing from the blood to the lungs is equal to the amount of oxygen removed from the blood in a given time (2). Conversely, any significant disagreement in the actual manifestations of hypoxia at altitudes which are equivalent as to their tracheal oxygen pressures would indicate differences in alveolar blood gas exchange (3).

We have applied these considerations to the available data on rapid decompression to high altitudes using air and oxygen. In the following analysis of these data pertinent to the interpretation of our own investigations we have made the assumption that the survival time at altitude bears a direct relationship to the hypoxia induced by decompression.

Extensive studies have been carried out by Clamann (4), Lutz (5) and Gelfan *et al.* (6) on small animals to ascertain the survival time on exposure to sudden decompression to various altitudes. Their results are consistent in that the survival time decreases with increasing altitude but reaches a minimum which remains constant regardless of further increase in altitude (Minimal Survival Time: MST). Lutz (5) compared the survival time of animals when they were exposed to rapid decompression in oxygen and in air. In the series breathing *oxygen* he found that a MST of 25 seconds was attained when the animals were decompressed to an altitude of 52,000 feet. Following the same procedure to altitudes below 52,000 feet the survival times were longer, and to altitudes above 52,000 feet the survival times did not become significantly shorter but remained about 25 seconds. In the series breathing *air* a MST of 25 seconds was reached on rapid decompression to 43,000 feet or above. In personal experiences on themselves Benzinger and Hornberger (7) obtained a very similar relationship for the 'Time of Useful Consciousness' (TUC) after explosive decompression to high altitudes breathing oxygen or air.

In the experiments mentioned above, MST was manifest on the average at 52,000 feet with pure oxygen. The tracheal oxygen pressure at that altitude (B = 79 mm. Hg) is:

$$pO_{2trach} = (79 - 47)\ 1.00 = 32 \text{ mm. Hg.}$$

The 'equivalent altitude' breathing air is obtained by solving *equation 1* for barometric pressure (B) when pO_{2trach} is 32 and F_{O2insp} is 0.209.

$$B = \frac{32}{0.209} + 47 = 200 \text{ mm. Hg.}$$

This barometric pressure represents an altitude of 32,600 feet in the Standard Atmosphere. In the experiments breathing air, however, MST was actually attained below 43,000 feet. This is surprising because the resulting treacheal oxygen pressure under these circumstances (B = 122 mm. Hg) is:

$$pO_{2trach} = (122 - 47)\ 0.209 = 15.7 \text{ mm. Hg.}$$

Table 1 summarizes the data given above.

Evidently MST occurs at much lower tracheal oxygen pressures when air is breathed. This discrepancy in the customary relationship between tracheal oxygen pressures and hypoxic effects breathing air and oxygen suggested that the composition of alveolar gas changes rapidly during and after sudden decompression in a manner giving relatively high alveolar oxygen values compared to tracheal oxygen values while breathing air. Convincing evidence for this deduction was to be gained only by direct sampling of alveolar gas immediately after rapid decompression, thereby ascertaining in part the conditions for gas exchange in the lungs themselves.

TABLE 1. RELATIONSHIP BETWEEN TRACHEAL OXYGEN TENSION AND SURVIVAL TIME IN MICE AFTER RAPID DECOMPRESSION BREATHING OXYGEN AND AIR (LUTZ)

ALTITUDE	(B-47) $F_{O_2 in} = pO_{2trach}$			AVERAGE SURVIVAL TIME
			mm. Hg	*sec.*
52,000 ft. breathing O_2	79 − 27 = 32	1.00	32	25
32,600 ft. breathing air	200 − 47 = 153	.209	32	80
43,000 ft. breathing air	122 − 47 = 65	.209	15.7	25

PROCEDURE

A 'parasite compartment' for rapid decompression was designed large enough to accommodate one man in the sitting position. It was attached to a large decompression chamber by a pipe 12 inches in diameter. As the volume proportion of the two chambers was 1:40 the smaller compartment could be decompressed to a simulated altitude of 60,000 feet within 2 seconds if the larger one had been previously reduced to 20 mm. of Hg total pressure. The connection was established by means of a simple knife-valve operated by hand on the connecting pipe. The barometric pressure in the parasite compartment was recorded continuously during the experiments on a photokymograph with automatic timing and markings for alveolar samples, etc. The subject breathed through a rubber mouthpiece attached to inspiratory and expiratory valves. A nose clamp was worn throughout. The alveolar samples were obtained at the end of forced expiration in evacuated burettes through a small rubber tube leading to the base of the tongue by the subject in the chamber and analyzed in the Haldane apparatus. Base-line values were taken regularly shortly before decompression sitting in the chamber and between 2 and 5 seconds after rapid decompression to the peak altitude. In the series using oxygen which was administered from a Douglas bag outside the chamber through a demand regulator it was necessary to start from a base level of 3300

TABLE 2. COMPOSITION OF DRY ALVEOLAR GAS 2–5 SECONDS AFTER RAPID DECOMPRESSION BREATHING AIR

NO. OF EXPERIMENTS	ALTITUDE TO WHICH DECOMPRESSED	O_2	CO_2	N_2
	ft.	%	%	%
69	Ground level	14.3	5.6	80.1
3	16,400	13.7	8.9	77.3
2	19,700	14.4	11.1	74.5
3	21,700	14.8	11.8	73.5
3	23,000	15.0	10.8	74.2
2	26,300	15.3	14.8	69.9
1	29,500	15.4	16.4	68.2
4	31,200	16.3	17.7	66.0
2	32,800	19.3	22.3	58.4
6	33,000	19.8	22.0	58.0
5	34,500	20.5	24.2	55.8
6	39,500	23.7	30.7	45.6
1	40,000	23.4	29.1	47.5
2	45,900	24.7	41.6	34.4
2	46,000	26.0	42.0	32.0
3	50,000	27.0	40.3	32.7

The values other than those for ground level were taken 2–5 seconds after the rapid decompression to the various altitudes represented.

The figures given represent single samples or mean values as indicated.

Ground level controls were taken immediately before decompression in all experiments.

TABLE 3. COMPOSITION OF DRY ALVEOLAR GAS 2–5 SECONDS AFTER RAPID DECOMPRESSION BREATHING OXYGEN

NO. OF EXPERIMENTS	ALTITUDE TO WHICH DECOMPRESSED	O_2	CO_2	N_2	
	ft.	%	%	%	
2	32,900[1]	71.7	19.5	8.8	
3	32,900	70.6	23.4	6.0	
3	39,400[1]	73.2	22.8	4.0	
3	39,400	72.0	23.6	4.4	
3	42,700	72.8	24.0	3.2	base level 3,300 ft.
3	44,300	66.4	28.0	5.6	
2	47,600	65.4	31.0	3.6	
1	50,000	58.0	38.8	3.2	
1	50,000	50.6	44.2	5.2	
1	50,000[2]	50.6	45.8	3.6	
1	52,500[2]	40.0	56.2	3.8	base level 33,000 ft.
1	52,500[2]	41.0	56.0	3.0	

[1] Samples were taken 5–6 seconds after decompression.

[2] In these three instances the subjects were rapidly decompressed from a pressure altitude of 33,000 feet to the higher altitude shown. In the other tests with oxygen the rapid decompression was effected from 3300 feet to the higher altitude.

The nitrogen fractions listed are probably due in part to slight admixtures of air at the inspiratory port. For this reason it is impossible, unfortunately, to estimate nitrogen elimination from these figures.

feet because a small pressure difference was required to operate the reducing valve of the regulator. In several experiments to 50,000 feet and above, the base level was raised to 33,000 feet and maintained for 10 minutes breathing oxygen to alleviate disturbances due to the expansion of intestinal gas in subsequent decompression to greater altitudes. No incapacitating impairment due to trapped gas or ear trouble was experienced during the entire series of 75 experiments in which pressure differentials up to 600 mm. Hg (11.6 p.s.i.) were applied in 2 seconds. On rare occasions fits of coughing set in after forced expiration at altitude for alveolar samples. This irritation persisted for several hours after returning to ground level. No changes were detected in the lungs by x-ray examination on the same day.

RESULTS

In evaluating the data presented in tables 2 and 3, showing the composition of alveolar gas within the first few seconds after rapid decompression breathing air or oxygen, it must be kept in mind that each of these findings represents a momentary phase in a rapidly changing course of events and not a steady state. Considerable variations in samples taken at the same altitude in different experiments were to be expected. Taken in their entirety, however, each of the two series shows significant trends.

After decompression breathing air (table 2) there is a marked increase in alveolar carbon dioxide, rising from 5.6 volumes per cent at ground level to over 40 volumes per cent at 50,000 feet. The percentage of oxygen in the lungs does not show appreciable changes at altitudes below 30,000 feet. At 34,500 feet, however, the alveolar oxygen approximates that of ambient air. Any suspicion of a sampling error was dispelled by the consistently high carbon dioxide values in the same samples. In all tests above 39,500 feet the samples definitely contained more oxygen than does inspired air reaching 27 volumes per cent at the highest altitude in this series. The results show that the normal composition of alveolar gas is almost completely inverted at 50,000 feet, a large part of the nitrogen being replaced by carbon dioxide and oxygen.

The situation is different, however, when oxygen is breathed before rapid decompression (table 3). In addition to water vapor there are only 2 rivals for alveolar space: carbon dioxide and oxygen. With increasing altitude carbon dioxide encroaches more and more on the oxygen and gains more than half the lung space available for gas at 52,500 feet.

DISCUSSION

Under normal respiratory conditions the composition of alveolar gas is maintained constant by a balance between the exchange of metabolic gases with the blood and the alveolar ventilation. Theoretically the primary effect of rapid decompression would be to reduce the density of all gases present in the lungs

in equal proportion. This reduction of density in itself would not bring about changes in the relative composition of gas. Significant alterations in the relative proportion of the various gases must be the result of simultaneous and subsequent blood-alveolar gas exchange and of adjustments of respiration.

According to our data there must be an appreciable discharge of carbon dioxide from the blood in a very short time accompanied by a sharp decline in the uptake of oxygen. Since more oxygen was found in the lungs than is present in air above 40,000 feet when only air was inhaled, the oxygen must necessarily have passed back from the pulmonary blood into the alveoli. Any respiratory movements which may occur seem to have very little effect on the alveolar gas composition under these conditions since carbon dioxide and oxygen predominate over nitrogen.

In the absence of any inert gas when breathing oxygen it is not possible to estimate the oxygen uptake from the alveolar data nor to determine if and when a reflux of oxygen into the lungs takes place, as is the case when breathing air. The oxygen found in the alveolar samples may originate from the blood or the inspired gas. Whatever amount of oxygen may be released from the blood, its amount is certainly surpassed by the profuse discharge of carbon dioxide.

The physiological significance of the remarkable changes found in the composition of alveolar gas after rapid decompression cannot be fully appreciated without ascertaining the effective tension of each of the components in their relationship to the gas tensions in the blood passing into the lungs.

Gas Tensions. In calculating the partial pressures of oxygen and carbon dioxide at the time the samples were taken, it is necessary to make an important reservation: Is it permissible to assume complete water vapor saturation at body temperature under the conditions of the experiment? During sudden decompression a large part of the total gas content of the lungs is expelled including a proportionate amount of water vapor. We do not know if complete saturation is regained immediately, especially in view of the hyperventilation which ensues. We hope to obtain more information on this point in a current study with a new device for measuring water vapor saturation in small samples in which the dew point is determined thermo-electrically. For the present we may assume full saturation in our samples and calculate the partial pressures in the customary manner as

$$pO_{2alv} = (B - 47)\, Fo_{2alv} \qquad (2)$$

in which B = barometric pressure.
47 = water vapor pressure in mm. Hg at 37° C.
Fo_{2alv} = fraction of oxygen in alveolar gas.

In figure 1 the partial pressures of oxygen and carbon dioxide are plotted against barometric pressure and altitude from the data in tables 2 and 3 con-

trasting the conditions breathing air and oxygen. The benefit gained by breathing oxygen as compared to air is very striking in the alveolar oxygen tensions obtained at moderate altitudes but becomes much less impressive at

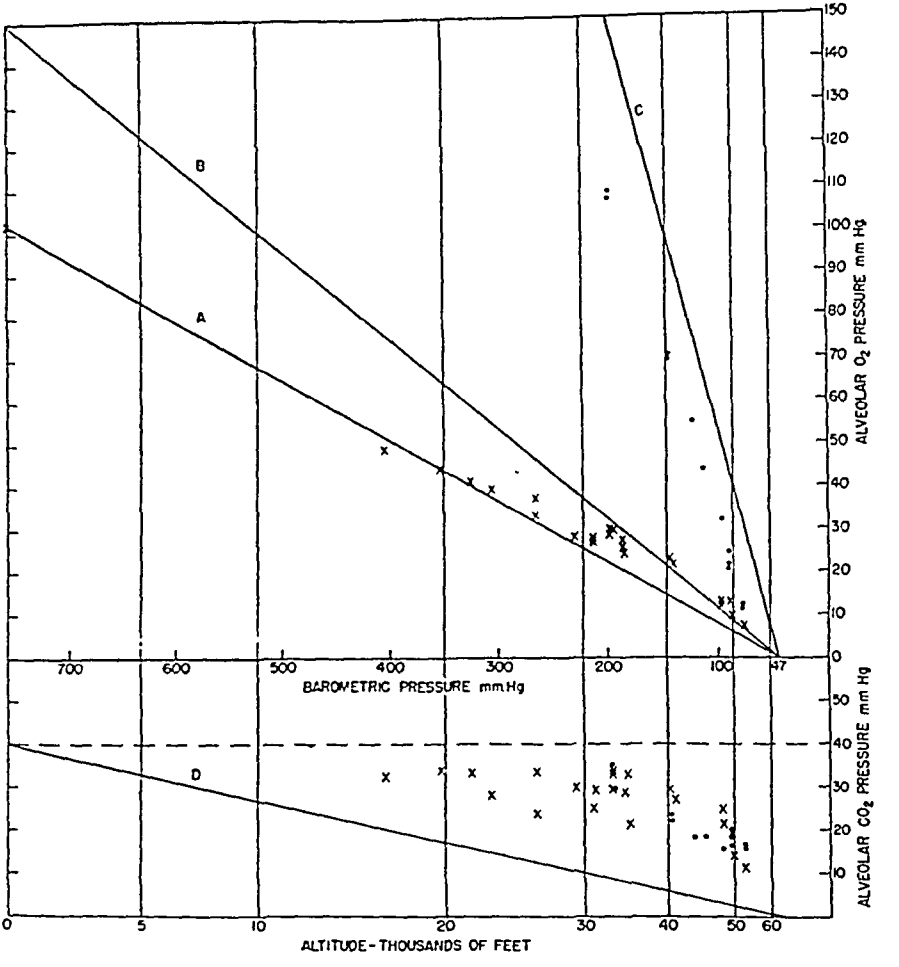

Fig. 1. ALVEOLAR OXYGEN AND CARBON DIOXIDE pressures immediately after rapid decompression breathing air (x) and breathing oxygen (·) at altitudes up to 52,500 feet. Lines of reference: *A*. Theoretical alveolar oxygen pressure calculated for a volume fraction of 0.143 oxygen, as present at ground level before decompression = (B − 47) 0.143. *B*. Tracheal oxygen pressure breathing air calculated as = (B − 47) 0.209. *C*. Tracheal oxygen pressure breathing oxygen calculated as = (B − 47) 1.00. *D*. Theoretical alveolar carbon dioxide pressure calculated for a volume fraction of 0.056 as present at ground level before decompression = (B − 47) 0.056.

40,000 to 50,000 feet and above. The main reason for this is obviously the reduction in total pressure which brings the partial pressures closer together in both cases. In addition it is noticeable from figure 1 that the alveolar oxygen pressure of the individual breathing air gradually gains ground on the

subject with oxygen above 33,000 feet. This is due to carbon dioxide and oxygen from the blood entering the alveoli and partly displacing the nitrogen there. Part of the oxygen from the blood is trapped in the lungs and a higher oxygen pressure is maintained at the blood-gas barrier than would be the case if the barrier were directly exposed to the ambient atmosphere. It appears that the oxygen issuing from the blood is not entirely lost to the organism but temporarily builds up the alveolar oxygen pressure to a level higher than that in the environment.

Such a situation certainly cannot arise when pure oxygen is inhaled. In this case any blood gases originating from the pulmonary capillaries can displace only oxygen and carbon dioxide. Since the latter is predominant, the alveolar oxygen pressure remains well below that in the trachea (fig. 1*C*). The tendency of the alveolar oxygen pressure in the man breathing air to approach that of the subject using oxygen continues up to approximately 52,500 feet where they are practically identical.

Considering these changes in alveolar gases it may be understood why it is not possible to predict 'equivalent altitudes' in rapid decompression by calculating equal *tracheal* oxygen pressures as we pointed out for the survival time in table 1. By interpolating the *alveolar* oxygen pressures in figure 1 for the altitudes at which minimal survival time was reached breathing air (43,000 feet) and oxygen (52,000 feet), a much closer agreement is found. In both cases the alveolar oxygen pressure would be 18 to 20 mm. Hg.

In rapid decompression to altitudes above 52,500 feet it is irrelevant, as far as immediate hypoxic effects are concerned, whether air or oxygen is breathed. This, however, by no means signifies that it is useless to supply oxygen under these conditions. On the contrary the chances of survival and revival for an aviator exposed to explosive decompression in the stratosphere will depend mainly on his being connected to his oxygen apparatus in this emergency and during descent. Recompression under these conditions has the effect of one very deep inspiration. Gas is pressed into the lungs regardless of respiratory movements. If pure oxygen is available, adequate conditions for survival on descent will be reached around 44,000 feet. Breathing air, consciousness may not be regained if a descent below 25,000 feet is not accomplished quickly enough.

Gas Diffusion. Under the experimental conditions used in this study it is possible to vary the gas tensions instantaneously at the alveolar gas-blood barrier, thereby forestalling any respiratory or cardiovascular adjustments of the organism more effectively than by any other procedure to produce acute, severe hypoxia in animal experiments. Fulminating hypoxia has frequently been induced for this purpose either by suddenly replacing pure oxygen by air at high altitudes or by administering 100 per cent nitrogen at ground level. Both these procedures involve an uncertain period of time for intrapulmonary

mixture which depends mainly on the respiratory volume and considerably delays hypoxia of the blood and tissues.

In rapid decompression or recompression gas tensions in the lungs change so abruptly that the alveoli act in the manner of an aerotonometer in which oxygen can be shuttled back and forth across the alveolar membrane by reversing the pressure gradient for diffusion. Taking, for example, an experiment in which the alveolar oxygen was 14.3 volumes per cent at ground level, and 27.0 volumes per cent 5 seconds after decompression to 50,000 feet (B = 87 mm. Hg), the increment of oxygen in the lungs was 27.0 − 14.3 = 12.7 per cent of the alveolar gas volume. The lung volume of the subject was measured as approximately 3000 cc. at resting respiratory level, so that the increase in oxygen may be estimated as 3000 × 12.7/100 = 381 cc.

In this equation the alveolar air is assumed to be saturated with water vapor at 37° C. It represents the actual volume of oxygen increase in the lungs in 5 seconds at 50,000 feet. Reduced to Standard Temperature Pressure (STP) this amounts to:

$$\mathrm{Vol}_{STP} = \frac{87 - 47}{760} \times \frac{273}{273 + 37} 381 = 17.7\text{cc.}$$

The rate of flow for oxygen passing from the blood in these 5 seconds must have been at least: 17.7 × 60/5 = 212 cc./minute.

This figure which is not far below the normal rate of oxygen *uptake* certainly represents a minimum because part of the gas must have escaped to the environment. Admittedly arbitrary in detail this example shows that oxygen may flow freely through the alveolar membrane in either direction according to the diffusion gradient. More exact measurements of gas diffusion will have to include continual measurement of volume and composition of expired gas (8).

From the data provided in figure 1, one may predict at what altitude oxygen will start flowing back into the lungs if it is accepted that the oxygen pressure of mixed venous blood entering the pulmonary capillaries is 35 to 40 mm. Hg and that this tension is maintained for several seconds after decompression. At 32,800 feet (198 mm. Hg) breathing air the alveolar oxygen pressure drops to 30 mm. Hg establishing a pressure-head of 5 to 10 mm. Hg from the blood to the alveoli. Using oxygen a similar situation would not arise below 48,000 feet. A reversed pressure gradient of this kind cannot persist for any length of time. Due to the continuing utilization of oxygen, the oxygen tension of the blood returning to the lungs must fall below that of the alveoli very rapidly. A number of alveolar determinations (table 4) at 33,000 feet taken at different intervals up to 25 seconds in separate experiments breathing air demonstrate the very transitory nature of the conditions for gas exchange.

Each figure in table 4 represents the mean value to at least 3 experiments. During the first few seconds (A) the alveolar oxygen content is nearly as high

as in ambient air, probably due to the reflux of blood oxygen mentioned above. After 8 to 10 seconds (B) it has declined slightly accompanied by a rise in carbon dioxide and a further drop in nitrogen. Since the alveolar oxygen content has dropped to 17.7 volumes per cent after 20 to 25 seconds (C), it must be assumed that oxygen is again passing *into* the blood at this time, even if this implies that the pulmonary blood has less than 18 mm. Hg oxygen pressure. A simultaneous increase in pulmonary ventilation indicated by a lower carbon dioxide and higher nitrogen level which would tend to raise the oxygen level, only emphasizes this interpretation. Incidentally the proportion of 64 volumes per cent nitrogen present in the lungs at 20 to 25 seconds shows that the stream of carbon dioxide released from the blood is still much greater than the oxygen uptake. In fact the 'alveolar R.Q.' (9) resulting from the data in table 4 C amounts to 2.5. This, of course, is no measure of the true combustion quotient in the body but merely demonstrates the 'non-steady state' of respiratory conditions.

TABLE 4. COMPOSITION OF ALVEOLAR GAS AND GAS TENSIONS AT DIFFERENT TIMES AFTER RAPID DECOMPRESSION TO AN ALTITUDE OF 33,000 FEET BREATHING AIR

TIME OF SAMPLE	O_2	CO_2	N_2	IN MM. HG		
				pO_2	pCO_2	pN_2
	%	%	%			
A = 2–5 sec.	20.05	19.6	60.35	30.25	28.0	118.5
B = 8–12 sec.	19.1	22.8	58.1	28.5	33.0	114.0
C = 20–25 sec.	17.7	18.3	64.0	18.0	25.0	125.5

Hypocapnia. In view of the far-reaching effects of any substantial loss of carbon dioxide from the blood on its oxygen saturation, on *p*H, and on cerebral blood flow and cell metabolism, it is important to estimate the extent of hypocapnia caused in the blood in rapid decompression. Although all alveolar samples indicated a very marked increase in the volume fraction of carbon dioxide, the carbon dioxide pressures calculated from the samples (fig. 1) were consistently below the average at ground level, and dropped to near 15 mm. Hg at 50,000 feet.

The question arises whether the blood passing through the lungs in this case reaches an equilibrium with the alveolar carbon dioxide as is generally accepted for normal conditions. According to the investigations of Luckner (10) the unloading of carbon dioxide appears to be rapid enough to ensure complete equilibrium in less than 1 second within a wide range of carbon dioxide tensions and independent of the oxygen saturation of the blood. The average time spent by the blood in the pulmonary capillaries is of the same magnitude (11). We do not know if this is true in rapid decompression. However, if we assume the carbon dioxide tension in the pulmonary vein to be equal to the

alveolar tension, we may attempt an approximate calculation of the amount of carbon dioxide passed from the blood into the lungs, provided the carbon dioxide content of pulmonary arterial blood does not change appreciably by recirculation within the 5 seconds that elapsed between rapid decompression and the alveolar sample. In table 5 the carbon dioxide output in the lungs is derived from the alveolar carbon dioxide pressure as measured at 50,000 feet based on a normal pulmonary blood flow of 4800 cc/min. The arterial carbon dioxide content was determined from a carbon dioxide absorption curve of blood taken from the subject of this experiment at ground level allowing for changes in capacity due to the simultaneous reduction in oxygen saturation at altitude (12). It appears that the amount of carbon dioxide released from the blood at 50,000 feet is three times greater than in the same time in resting conditions at ground level. There can be no doubt that the blood passing through the lungs becomes severely hypocapnic immediately after rapid decompression at great altitudes to an extent reproducible only by forced breath-

TABLE 5. PASSAGE OF CARBON DIOXIDE INTO THE LUNGS AT GROUND LEVEL (A) AND IMMEDIATELY AFTER RAPID DECOMPRESSION TO 50,000 FEET (B)

	MIXED VENOUS BLOOD		ALVEOLAR EQUAL ARTERIAL BLOOD		CO_2 DIFFERENCE VEN. — ART.	CO_2 PER MIN.
	Content	Tension	Content	Tension		
	vol. %	*mm. Hg*	*vol. %*	*mm. Hg*	*Vol. %*	*cc.*
A	53	45	48	40	5	240
B	53	45	38	15	15	720

The above is calculated from the alveolar carbon dioxide tension and the carbon dioxide absorption curve for a pulmonary blood flow of 4800 cc. per minute.

ing over a period of many minutes. A considerable rise in blood *p*H is inevitable.

Hypocapnia is well known as an attendant phenomenon of mild and severe hypoxia and is generally accepted to be the result of hyperventilation due to the hypoxic stimulus. In rapid decompression carbon dioxide is lost from the lungs in considerable quantities before any adjustments of respiration come into play. In this case hypoxia and hypocapnia are completely simultaneous.

SUMMARY AND CONCLUSIONS

During and immediately after rapid decompression to high altitudes breathing *air* the composition of alveolar gas undergoes changes involving an increase in the volume fractions of carbon dioxide and oxygen and a decrease in nitrogen. At altitudes above 39,400 feet more oxygen was present in the lungs than in the ambient atmosphere.

While breathing *oxygen* in similar experiments the alveolar oxygen fraction was partly displaced by carbon dioxide which comprised more than half of the lung gas content at 52,500 feet.

By relating the alveolar gas pressure to the altitude it is shown that the benefit gained by breathing oxygen at moderate altitudes is less pronounced in rapid decompression to higher altitudes. This is not only the result of the reduction in total pressure but also due to the relatively high oxygen content in the lungs after decompression breathing air, where oxygen from the blood returns to the lungs and temporarily augments the alveolar oxygen pressure at the expense of nitrogen. In effect there is little difference in alveolar oxygen pressure whether breathing air or oxygen in rapid decompression to altitudes above 52,500 feet. Nevertheless the decisive importance of breathing 100 per cent oxygen previous to and continuously after decompression for the chances of survival on descent is emphasized.

In rapid decompression 'equivalent altitudes' cannot be estimated from tracheal oxygen tensions as these do not reflect the conditions in the lungs.

On applying the data obtained in this study to previous comparable investigations on rapid decompression, it appears that survival time and time of useful consciousness reach a minimum and remain constant at altitudes where the alveolar oxygen pressure drops below 18 to 20 mm. Hg. Evidence is presented that oxygen passes back into the alveoli from the blood in the pulmonary capillaries whenever the alveolar oxygen pressure is lower than that of mixed venous blood. The low carbon dioxide pressures encountered immediately after rapid decompression indicate that hypocapnia of the blood is not a secondary event but is simultaneous with hypoxia under these conditions.

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Biophysical Requirements for the Ventilation of Clothing

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PHYSIOLOGICAL REGULATION and insulative clothing are insufficient protection against very high temperatures, common in industry and in the armed services, and against the widely and rapidly varying temperatures peculiar to aircraft operations. Electrically heated clothing broadens the comfort range of clothing for low temperatures; but air crews especially may spend much time in warm or even hot environments before exposure to cold. It will be shown herein that air of the proper temperature blown under the clothing near the skin can protect against high, low and changing temperatures. The ambient environment is replaced with an individual environment of roughly one cubic foot per man; and the function of the outer clothing is changed from insulation of the man to insulation of the ventilating air. Because of this, outer clothing may be chosen for its functional suitability, and not necessarily for its insulation; for example, vapor impermeable outer garments offer no problems of thermal comfort. The chief limitation, as of electrically heated clothing, is the necessary connection to a power source.

The purposes of this paper are to define the ventilation requirements for maintenance of thermal balance, in the range $-30°$ F. to $+180°$ F.; and to point out the potential usefulness of internally ventilated clothing both as a tool of physiology and as a solution to many industrial and Service problems of thermal protection.

The idea of blowing or circulating air under clothing is not new. In 1904 a patent was granted on a 'Body Ventilating Apparatus' (1) and a number of others have been issued since. However, it is only within the last few years that there has been any persistent construction and testing of ventilating suits. Houghten *et al.* (2) in 1941 reported increased comfort and efficiency of workers

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in hot environments when a simple ventilating coverall was worn. Their report set forth some of the physical principles of the system. During World War II an Australian group designed and tested a ventilating harness and air supply system for use in tanks at temperatures of about 100° F. From 1943 to 1945 the Armored Medical Research Laboratory reported the experimental use of ventilated garments designed for use in tanks (3). The Royal Canadian Air Force improved a Royal Air Force airheated undersuit; by 1945 a suit which heated the hands, feet and back had been developed which gave some protection down to −30° F. as judged by subjective sensations and skin (but not rectal) temperatures (4). An extensive series of tests of several ventilating garments was reported in 1945 by the Aero Medical Laboratory (5). These tests were made to select a suit, and air flow and temperature, for men doing moderate work for limited periods at 165° F. in the Climatic Hangar of the Air Proving Ground Command. Several ventilated suits have been manufactured by the Strato Equipment Company of Minneapolis and the Carrier Corporation of Syracuse, but regular use of such equipment is not known to the authors.

Previous studies have been primarily tests of equipment intended for specific purposes. The present paper is concerned with what any clothing ventilating system must do to insure comfort with variation of the ambient temperature, amount of outer clothing and activity. It is not concerned with the mechanics of the system. The experiments discussed herein were designed to keep men comfortable at ambient temperatures ranging from −30° F. to +180° F. when clothing intended for use at 40 or 50° F. was worn; and with hands and feet heated or cooled only by their blood supply. Since the experiments were planned to maintain thermal balance, neither a control series nor a definition of tolerance was required.

THEORY

The essence of the problem is the determination of the heat content change of the ventilating air for any combination of insulative clothing, ambient conditions, and metabolic level. The general relation between the rate of heat uptake of the ventilating air, the rate of heat loss by the body, the rate of heat leakage through the clothing, and the rate of change of the heat content of the body may be written:

$$\Delta H_v/t = Q_b/t - Q_o/t - \Delta H_b/t \qquad (A)$$

Where:

ΔH_v is the change in heat content (enthalpy) of the ventilating air. This is taken as positive when the heat content of the air increases.

Q_b is the sensible heat loss of the body; i.e., the difference between the total metabolic heat, Q_m and evaporative heat loss, Q_e.

Q_c is the heat leakage through the clothing. This is taken as positive when the direction of heat flow is outward.

ΔH_b is the change of heat content of the body. Contrary to some terminology, this is defined as being positive when the heat content of the body increases.

t is time.

An expression for the rate at which heat should be supplied or removed from the man to maintain thermal balance was found to be useful. This is designated as the 'steady state heat surplus', $Q\sigma/t$, and is defined by the relation:

$$(B) \qquad Q_\sigma/t = Q_b/t - Q_c/t;$$

that is, the steady state heat surplus is the difference between the sensible heat loss of the body, and the heat leakage through the clothing. At low ambient temperature $Q\sigma/t$ is negative—heat must be supplied—and at high temperatures, it is positive. For thermal balance $\Delta H_v/t$ should equal $Q\sigma/t$.

The rate of increase in heat content of the ventilating air, $\Delta H_v/t$, is defined by the equation:

$$(C) \qquad \Delta H_v/t = (W_v/t)\, C_v\, (T_{v2} - T_{v1}).$$

Where:

W_v/t is the flow rate of the air in weight units per unit time.

C_v is the specific heat of the air at constant pressure.

T_{v1} and T_{v2} are the temperatures of air entering and leaving the garments, respectively.

The rate of heat loss through the clothing, Q_c/t, is determined by the insulation of the clothing worn over the ventilating air, and by the environmental conditions. This relation may be expressed by the clo equation of Gagge, Burton and Bazett (6):

$$(D) \qquad Q_c/t = \frac{k_c A_c (T_c - T_o)}{I}.$$

Where:

k_c is the constant for conversion to clo.

A_c is the area of the clothing layer just outside the ventilating air, i.e., of the barrier coverall described below.

T_c is the average barrier coverall temperature.

T_o is the operative temperature (7).

I is the insulation (in clo) of the outer clothing (I_c) plus the insulation of the ambient air (Ia); i.e.,

$$(E) \qquad I = I_c + I_a$$

The temperature and the area of the barrier coverall rather than of the skin are used in *equation D* because the outer clothing primarily insulates the air, and not the man, from the environment. It is obvious from *equations A* and *D* that $\Delta H_v/t$ will vary inversely with the insulation. The rate of heat leakage

through the clothing becomes large when T_a differs significantly from T_c. (When the man is comfortable, T_c is relatively constant over the wide range of ambient temperatures studied, as will be shown.)

A relation may be derived between the steady state heat surplus, Q_s/t, and the insulation underlying the ventilating air (or other source of heat or cold) and the overlying insulation, I_a and I_o respectively. The following is a variant of the derivation reported to the Canadian National Research Council by A. C. Burton in 1943.

$$(B) \qquad Q_s/t = Q_b/t - Q_o/t.$$

Q_d/t may be given for the steady state as

$$(a) \qquad Q_b/t = \frac{k_o A_u (T_s - T_v)}{I_u},$$

where A_u is the area of the underlying garments, T_s is average skin temperature, and T_v is average ventilating air (or electrically heated suit) temperature.
Q_o/t is defined by

$$(b) \qquad Q_o/t = \frac{k_o A_o (T_v - T_o)}{I_o},$$

where A_o is the outer garment area and T_o is the average temperature of its outer surface. Substituting the expression for T_v from (*a*) into (*b*), assuming that $A_u = A_o$ or that an intermediate value, A_n, is used, and substituting the resultant expression for Q_o/t into (*b*) gives:

$$(c) \qquad Q\sigma/t = Q_b/t\,(1 + I_u/I_o) - \frac{k_o A_n (T_s - T_o)}{I_o}$$

This equation may be written more exactly as a summation of the several body regions. It is to be noted that no assumption is made concerning direction of heat flow.

The definition of clo involves the subtraction of the insulation of the air from the total insulation (6), which implies that insulations in clo are additive. However, since clo is defined as a temperature difference per unit rate of heat production *per unit area*, they are strictly additive only if increased thickness of insulation does not change the outer area, i.e., for flat surfaces. The usual practice is to determine I_o and I_a separately; I_o from the clo equation and I_a from an empirical equation, e.g. (8). This procedure has been followed in the calculations to be described. The insulation of the outer clothing was determined upon an electrically heated copper manikin (9) with that clothing layer just outside of the ventilating air placed next to the heated surface of the manikin. It is to be noted that when the requirements established by these experiments are used, insulation must be determined in a like manner. The error in the addition of I_a to I_o is due to the variation of outer clothing area with different clothing assemblies. The absolute value of this error increases with increasing thickness of the clothing, but, since I_a is small compared to I_o, the relative error may decrease with heavier clothing. There are other factors which are not considered in *equations A* and *C* because they are within the

limits of error of the experiments to be described. These are the change in heat content of the clothing, the change in kinetic energy of the ventilating air, and any Joule-Thomson effect. Variation of the humidity of the ventilating air is of little importance, since its effect on specific heat is within the limits of experimental error. The principal humidity requirement is that the vapor pressure of the water in the ventilating air be somewhat below the vapor pressure of water at skin temperature.

Physiological strain may be evaluated by measurement of changes of body temperature as determined by Burton's (10) equation, by the sweat rate, and by subjective comments. (It will be shown in the paper following this that the temperature of the hands and feet is also a good indication of such strain.) Whether or not a given physiological adjustment causes discomfort may depend upon the experimental conditions. Thus, while accumulation of sweat in clothing is uncomfortable, moderately increased sweating in a ventilated system is not, since evaporation is rapid to the internally circulating air. The subjective effect of vasoconstriction in the hands and feet depends upon whether or not these parts are externally heated. A change of body heat content of ±10 Cal. usually produces no discomfort.

In a physical system, a given $\Delta H_v/t$ can be achieved by wide variation of both the air flow and temperature. In a physiological system, the temperature range of the ventilating air is limited. According to Moritz and Henriques (11), air hot enough to raise skin temperature to 120° F. will produce hyperemia in 8 minutes and epidermal necrosis in 10 minutes; and when skin temperature is 111° F., hyperemia occurs in 5 hours and epidermal necrosis in 6 hours. Discomfort due to chilling at the ventilating air inlet openings will result if very cold air is used. To make the best use of the ventilating air with a given thickness of clothing, there should be a minimum of insulation between the skin and the ventilating air, and the air should flow parallel to the skin and not transversely through the outer clothing.

METHODS

The experiments were done in the All-Weather Room of the Aero Medical Laboratory, at about 180, 120, 75, 0, −20, and −30° F. Air and wall temperatures were the same, so that operative temperature (7) was the same as dry bulb temperature. Air movement was such that the insulation of the ambient air, I_a, was the equivalent of 0.7 clo below 60° F.; at and above 60° F. it was 0.8 clo. Detailed descriptions of methods and calculations are given in Fetcher, Rapaport and Hall (12).

A ventilating assembly was designed to give reasonably good air distribution and to permit measurement of the temperature of the air leaving the clothing. It consisted of six rubber tubes supported inside a thin, air impermeable, barrier coverall. Drawstrings in the coverall divided the body into trunk,

arm, hand, foot, leg, and head regions and kept the air close to the skin. The head, trunk, arms, and legs had separate air supplies and air exhaust ports, permitting separate measurement of flow and inlet and outlet temperatures. The hands and feet were not ventilated, and care was taken to prevent leakage of air from the cuffs of the barrier coverall. This assembly was worn over long underwear equipped with thermocouples for skin temperature measurement. The insulation over the coverall was 2.1 clo in some cases, and 2.5 clo in others, as determined on an electrically heated manikin (9). The footgear insulation, calculated in clo, was 2.6; that of the gloves, 1.0. The flow distribution was generally in proportion to the area served, except that to the head; i.e., approximately 13 per cent to each arm, 25 per cent to each leg, and 24 per cent to the trunk. The head was not included in the general treatment because many factors other than activity and insulation influence its ventilation requirements. Since its area is about 8 per cent of the body area, that proportion of the sensible heat production was assigned to it, and subtracted from the total to give the sensible heat production of the rest of the body, Q_b'/t. (The body without the head will be written 'body'.)

Metabolic rate was measured in about one third of the experiments, but was found to vary only between 43 and 57 kg. Cal/hr/sq.m.; 50 Cal/hr/sq.m. was taken as the rate in the other experiments. Evaporative weight loss was measured in the experiments at room temperature and above; these measurements gave an average evaporative heat loss rate of 40 per cent of the metabolic rate for the experiments which maintained thermal balance; this percentage was assumed for the low temperature 'balanced' experiments, where weighings would have been unreliable because of the accumulations of condensed moisture. The exchange of heat between the lungs and the ventilating air was always negligible, except for evaporative loss, because the air was always temperate. Skin and rectal temperatures were measured at half-hour intervals. None of the variables of *equation A* was determined by difference.

RESULTS

Forty-three experiments were performed on 4 subjects; thermal balance was considered to have been maintained during 29 of these. The results of these 'balanced' experiments are summarized in table 1. Wherever the factor of area has entered into the calculations the results have been reduced to the area of the 'Air Force Man' (13). The corrections were small since our subjects ranged from 1.72 sq.m. to 1.90 sq.m., and the standard was taken as 1.84 sq.m. Detailed data are given in (12).

The first column of the table lists the number of experiments used in arriving at the average values given in the table. The second column is the ambient operative temperature, in this case equal to the dry bulb temperature. Column 3 is the insulation outside of the ventilating air, over trunk,

arms and legs, and includes the insulation of the ambient air. Column 4 is the average barrier coverall temperature, measured by 28 thermocouples. Column 5 gives the heat loss for the vasodilated hands and feet (Q_{h+f}) with gloves of 1.0 and boots of 2.6 equivalent clo (excluding air insulation). Column 6 is the observed enthalpy increase of the ventilating air, and column 7 is the steady state heat surplus calculated according to *equation B* from observed or assumed sensible heat loss rates, and from observed coverall temperatures. The values for the steady state heat surplus, in column 7, will be seen to be almost identical to the standard steady state heat surplus values given in column 8. These latter are calculated from a 'standard' sensible heat loss rate

TABLE 1. SUMMARY OF 'BALANCED' EXPERIMENTS

1 NO. OF EXPER.	2 T_o (°F)	3 I (clo)	4 T_c (°F)	5 $Q_h + f/l$ (CAL/HR.)	6 $\Delta\Pi_s'/l$ (CAL/HR.)	7 Q_σ'/l (CAL/HR.)	8 $\bar{Q}_\sigma'/l$ (CAL/HR.)	9 $\bar{Q}_\sigma'/l - \Delta\Pi_s'/$ (CAL/HR.)
6	182 ±3	3.3	86 ±2	−26 ±1	296 ±17	283 ±10	281	−15
6	121 ±1	3.3	86 ±2	−8 ±1	133 ±8	134 ±11	132	−1
3	73 ±2	3.5	88 ±1	+6 ±1	26 ±1	18 ±4	14	−12
3	73 ±1	2.9	86 ±1	4 ±2	22	24 ±6	17	−5
3	3 ±1	2.8	92 ±2	31 ±1	−224 ±17	−210 ±5	−205	+19
1	4	3.2	94	29	−183	−175	−176	+7
2	−18 ±1	2.8	93 ±1	37 ±2	−302 ±4	−262 ±2	−262	+40
1	−20	3.2	95	35	−239	−229	−237	+2
4	−31	3.2	95 ±1	40 ±2	−287 ±9	−263 ±2	−262	+25

of 51 Cal/hr. for the 'body' and from the standard heat loss rate through the clothing according to the equation.

$$(F) \qquad \bar{Q}_\sigma'/l = \frac{k_\sigma(\bar{T}_c - T_o)\,\bar{A}_c}{I} + \bar{Q}_{h+f}$$

Where:

$\bar{T}_c$ is the standard barrier coverall temperature, is taken as the average of the T_c's of the 'balanced' experiments.

$\bar{A}_c$ is the standard heat transfer area of a barrier coverall for the 'Air Force Man'.

$\bar{Q}_{h+f}$ is the standard heat loss from hands plus feet when these parts are vasodilated. The values used are the averages of the 'balanced' experiments.

The last column of the table shows the difference between the rate at which heat should have been removed and the rate at which it was being removed by the air. (Positive values mean that the surplus was being removed too slowly; that is, that the enthalpy of the body was increasing.) With two or three exceptions the differences are about the size of the experimental error. At low temperatures, it is apparent that there was a tendency to overheat the subjects; and a tendency at high temperatures to overcool them. This may be because both subject and operators were apprehensive of allowing the subject

to cool at low ambient temperatures, and to burn at very high temperatures. It will be shown in the following paper that overheating at low ambient temperatures is not required for comfort.

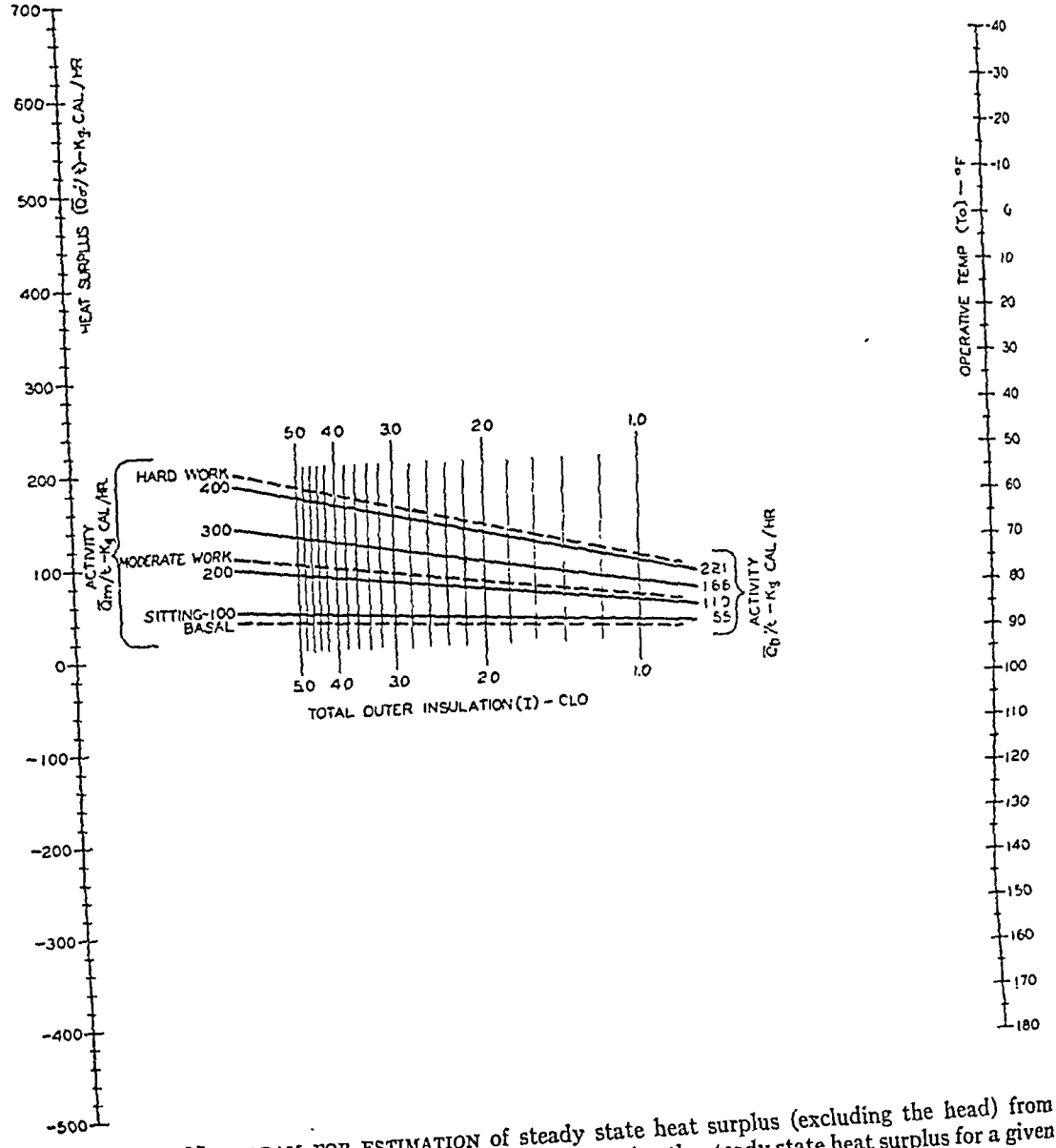

Fig. 1. NOMOGRAM FOR ESTIMATION of steady state heat surplus (excluding the head) from operative temperature, insulation and activity. To determine the steady state heat surplus for a given set of conditions, extend a straight line from the appropriate point on the operative temperature scale through the intersection of a vertical insulation line with the applicable metabolism line, to the heat surplus scale.

The standardized data may be expressed by the equation:

$$\bar{Q}\sigma'/t = \bar{Q}b'/t - 7.95\,\frac{(\bar{T}_c - T_o)}{I} \qquad (G)$$

in which the constant 7.95 includes not only k_p and A_c but also a correction for $\bar{Q}_{h+f}$. The condition that $\bar{Q}\sigma'/t = 0$ means that only enough air need be supplied to effect heat removal by evaporative cooling alone. A more useful form of *equation G* is given in figure 1. This nomogram is of general application for the determination of the steady state heat surplus, independently of the source of heat or of heat removal, provided the following conditions obtain; or that corrections are applied: *1*) The requirements of the head are not included, and no artificial heat is supplied to the hands and feet. *2*) The total outer insulation (clothing outside of the heat source including air) has been determined as described under METHODS. 3) The heat source is separated from the skin by less than one-half clo. *4*) The heat loss by evaporation is 40 per cent of the total metabolic rate, if the $\bar{Q}_m/t$ activity figures are used. (Q_b'/t values are also given for use when this is not the case.) *5*) The insulation of the gloves including air is between $1\frac{1}{2}$ and 2 equivalent clo, and the hands are not in contact with solid objects. *6*) The insulation of the footgear including air is greater than three equivalent clo. *7*) The area of the man is about 1.8 m^2.

Figure 1 shows clearly the influence of outer insulation upon the heat requirements. At an operative temperature of about 90° F. the clothing has no effect on the requirements, whereas at extreme temperatures its effect is great. The nomogram can also be used for the estimation of tolerance times if the total allowable body heat content change is known. The error of the chart is about 10 per cent or 10 Cal/hr.

Figure 1 was prepared on the assumption that T_c is constant at 90° F. Table 1 shows that T_c varies between about 86° F. and 95° F. for the 'balanced' comfortable experiments. The assumption does not apply to the comfort temperature for the coverall. In our experiments the subjects were too hot or too cold if the coverall temperature was more than about 2° above or below the averages given in table 1.

Figure 2 is a nomogram relating the change in heat content of the ventilating air to air flow and air inlet temperature. It is based on an empirical relation between the change of ventilating air temperature, ΔT_v, and the inlet air temperature, T_{v1}:

$$(H) \qquad \Delta T_v = (61.1 \pm 1.6) - (0.69 \pm .05)\, T_{v1}.$$

This was substituted in *equation C*. This chart is less reliable than figure 1, and it applies only to the ventilating assembly which we used. It is included to emphasize that, even with more efficient ventilating assemblies there will be rather definite limits to the rates at which heat can be supplied to the body; hence at extreme temperatures, as much as possible of the body surface must be ventilated; and appreciable insulation over the ventilating air is necessary.

On the other hand, requirements in the range +30° F. to +120° F. can be met with very simple equipment.

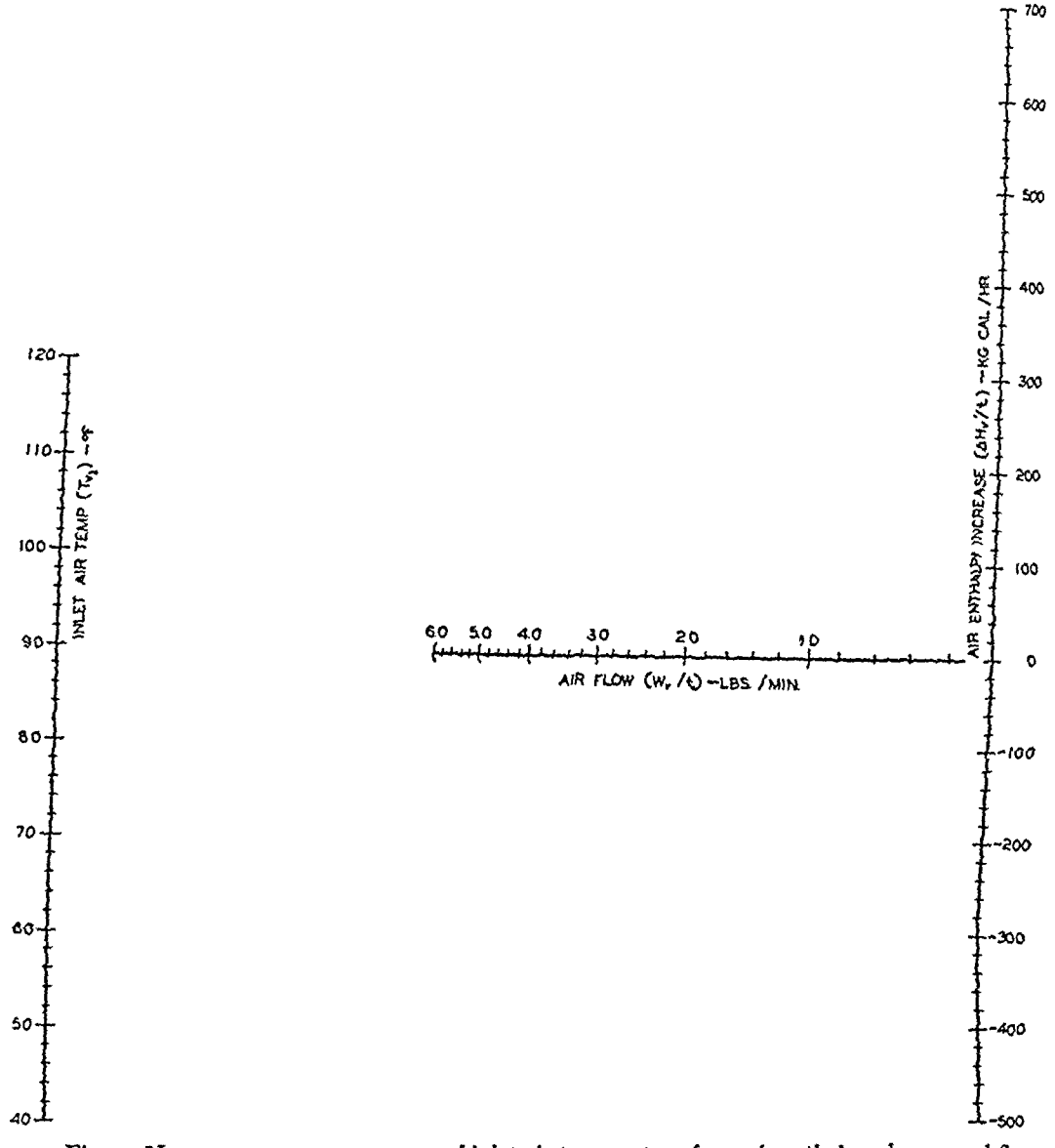

Fig. 2. NOMOGRAM FOR ESTIMATION of inlet air temperature from air enthalpy change and flow rate. (Limited to ventilating assembly described in text.) (To determine air temperature, extend a straight line from the given air enthalpy increase, which may be equal to the steady state heat surplus, to the given air flow, and thence to the air temperature line.)

As mentioned above, the head was not included in any of the estimates for mechanical reasons, although complete measurements were made of the ventilating conditions. A full helmet was used, reasonably air tight at the base of the neck; its insulation (excluding ambient air) was about 0.9 equivalent clo. It was suspended on an internal frame so that the ventilating air could

circulate freely around the head. At the extreme ambient temperatures, one-half pound of air per minute was found to be ample for comfort.

Two main avenues of development of ventilated clothing lie ahead: its development as a system of 'personal air conditioning' for the armed services and industry and its development as a physiological tool. The Service and industrial developments will require not only garment development, but development or adaptation of air source equipment in many instances; and control of air flow and temperature more or less automatically, depending on variability of ambient temperature, metabolism and insulation. However, control need not be precise, so that original calibration of a ventilating assembly to yield the information contained in figure 2 should provide a sufficiently accurate basis for adjustment of inlet air temperature and flow rate.

It will be apparent from the following paper that ventilated clothing has been useful as a physiological tool and that it has potentialities as an approximate calorimeter. Not only does it permit reasonably accurate quantification of thermal states and changes, but also it provides a flexible means of separate control of different body areas. It is quite possible that it may find application in physiological studies by virtue of this flexibility and its relative cheapness as compared to heated or refrigerated chambers. However, it is improbable that a single calibration of the ventilating harness (to relate inlet air temperature to the difference between inlet and outlet air temperatures) would give satisfactory accuracy for calorimetric studies. Therefore outlet air temperatures and separate air flows would have to be measured; which may be done as they were in the present study, but this method is cumbersome. Simplification of equipment and procedures is in progress, as well as construction of ventilating assemblies which distribute the air more effectively than present types.

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Control of Blood Flow to the Extremities at Low Ambient Temperatures

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THIS STUDY was undertaken to explore the extent of autonomic control of blood flow to the hands and feet. That is, to examine the question—is blood flow to the hands and feet at low ambient temperatures still regulated by the thermal state of the body as a whole, or is blood flow to the hands and feet determined by the known direct constricting effect of cold upon their blood vessels? Since the experiments of Sir Thomas Lewis in 1931 (1) there has been a growing understanding that vasodilatation may be produced in the extremities by heating other body areas. An intact sympathetic outflow to the extremity has been shown to be necessary for this reaction (1, 2). Pickering (3) suggested that the vasodilatation is the response to the circulation of warmed blood through the central nervous system, since it does not occur when the part heated is small or its circulation occluded. These observations have been confirmed repeatedly (4, 5). Recently, Miller has been able to prevent freezing of the rabbit's ear for two hours at $-55°$F. by warming the animal's body (6). The experiments reported herein reveal that a similar protection is available to the extremities of man. Inversely, Ferris and his co-workers (7) in particular have demonstrated that when the body is cooled, heating only the hand will not increase its blood flow over that of a non-heated hand.

The experiments were planned to investigate these specific points: *a*) The effect upon hand and foot temperatures of variation of heat supplied to the rest of the body. *b*) The effect of warming the body upon the temperature of extremities which had become cold. *c*) The differences in the temperature responses between the hands and feet. *d*) The effect upon hand temperature of a sudden increase in the cold stimulus applied to the hand when the body is warm.

METHODS

The main series of experiments was conducted at controlled ambient temperatures of about 0, -20 and $-30°$ F. in a cold room. Four young adult males served as subjects. They sat quietly throughout the experiments. The duration

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of the experiments was two hours or longer, unless there was rapid cooling of the extremities. The method of circulating air beneath clothing described in the preceding paper (8) made it possible to supply the body with as much or as little heat as was desired. It also permitted measurement of the rate at which heat was being supplied to the body, $\Delta H_v'/t$; and of the rate at which heat should be supplied or removed to maintain thermal equilibrium of the man: the 'steady state heat surplus' or $Q\sigma'/t$. A comparison of the two gave a quantitative evaluation of the thermal state of the body, within about 10 Cal/hr. Methods for the determination of these and other variables are outlined in the preceding paper and detailed in (9). The hands and feet received no artificial heat, being separated from the ventilating circuit by air-tight wristlets and anklets. These parts were heated only from their blood supply. Therefore, changes in their temperature indicated alterations in their blood flow. The thermal stress upon the body and the thermal stress upon the hands and feet could be varied independently; the former by variation of the hot air supply, and the latter by variation of the ambient temperature and insulation.

Average hand and average foot temperatures were measured by thermocouples connected in parallel. Those for the hand were located upon the ball of the first, third, and fifth fingers, and the palm and dorsum of the hand. Those for the foot were placed upon the ball of the great toe, the heel, the dorsum of the foot at the base of the first and fifth toes, and the dorsum of the foot just below the lateral and medial malleoli. Heavy footgear (insulation equivalent to 2.6 clo) and intermediate weight gloves (1.0 equivalent clo) were worn. In some experiments one glove was replaced with a rayon insert (0.25 clo) and in others, one hand was bared.

To extend the studies upon the fourth point, above, a supplementary series of experiments was performed in which the bare hand was put into a cold box. Each experiment consisted of two periods. In the first, the subject lay quietly in the nude at an ambient temperature of 65 to 74° F. for approximately 45 minutes, or until toe temperature approached within about 5° F. of the ambient temperature. With the body so cooled, one hand was inserted in the cold box and average hand and finger tip temperatures recorded. In the second period, the body was overheated by the use of an electrically heated blanket. When the subject was sweating, and the temperature of the toe of the uncovered foot had risen from about room temperature to above 89° F., the hand was again placed in the box and its temperature response followed.

RESULTS

Effect upon Hand and Foot Temperatures of Variation of Heat Supplied to the Rest of the Body. In 16 experiments over the temperature range from 0 to −30° F., it was found, without exception, that when the heat supplied was equal to or greater than the amount necessary for thermal equilibrium,

the average temperature of the hands and feet was maintained above minimum comfort level (70° F.). But, whenever the heat loss exceeded the heat supply by more than about 15 per cent both the hands and feet became cold, an indication of vasoconstriction. These experiments are summarized in table 1. Experiments listed as *A* and *B* were performed consecutively upon the same subject. In this table, T_0 is operative temperature. The values for $\Delta H_v'/t$ and $Q\sigma'/t$ are corrected to a standard surface area, and, for reasons mentioned in the previous paper, are for the body excluding the head. It is to be noted that the difference $Q\sigma'/t - \Delta H_v'/t$ is positive when there is an excess of heat supplied to the clothing, that is, when the body does not need to conserve heat; and negative when there is a net heat loss. The column headed '% Diff.' is calculated from $\frac{Q\sigma'/t - \Delta H_v'/t}{Q\sigma'/t} \times 100$.

The temperatures of the hands and feet in two experiments upon the same subject at 0° F. are shown in figure 1, which illustrates the main features of the data of table 1. In *experiment 7-15*, there was a net heat loss from the body of 72 Cal/hr. (41% of $Q\sigma'/t$). The hands and feet cooled rapidly; within 90 minutes hand temperature was 60° F. and the hands were painfully cold. Foot temperature dropped to approximately 75° F. In *experiment 8-7A*, the heat supply equalled the heat loss. Average hand and foot temperatures were maintained above 90° F.

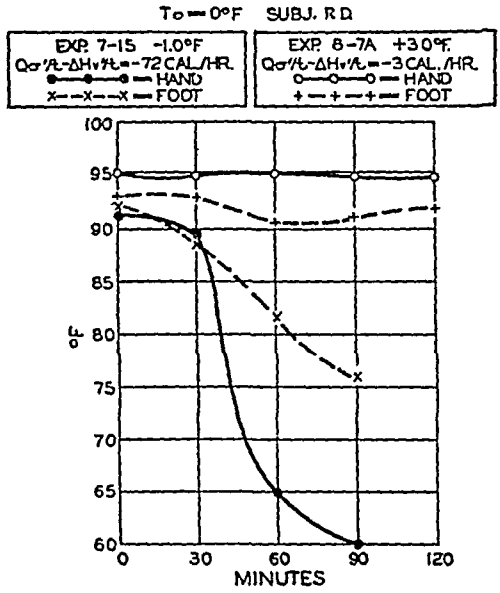

Fig. 1. HAND AND FOOT TEMPERATURES under conditions of thermal equilibrium and of high heat loss rate from the body. (Glove of 1.0 equivalent clo, and 2.6 equivalent clo boot.)

Effect of Warming the Body upon Cold Extremities. In four out of five experiments, extremities which had become cold could be rewarmed by heating just the body. One of the four is illustrated by figure 2, the graph of an experiment at 0° F., in which no heat was supplied for 45 minutes. Average hand temperature fell to 61° F. (finger tip temperature of 53° F.) and average foot temperature from 93 to 86° F. Heating was then begun, which reduced the net heat loss rate to 15 Cal/hr. Average hand temperature began to rise almost immediately and reached 90° F. within 55 minutes. Average foot temperature, however, continued to fall to 75° F. After

85 minutes, and concomitant with a reduction in the net heat loss rate to 6 Cal/hr., the average foot temperature began to rise and was 89° F. when the experiment was terminated. *In one experiment at* −30° F. ambient, the hand did not rewarm in spite of a heat excess of 39 Cal/hr. supplied to the body.

Differences between Temperature Response of Hands and Feet. When the heat supplied to the system exceeded heat loss, both the hands and feet were kept within the comfort range, that is above 70° F. In general, however, the average temperature of the feet was lower than that of the hands despite the greater insulation of the footgear. The difference varied from about 5° F. (*exper. 8-7A*, fig. 1; *expers. 9-9* and *9-10*, table 1) to 10 or 20° F. (*expers. 8-5A*,

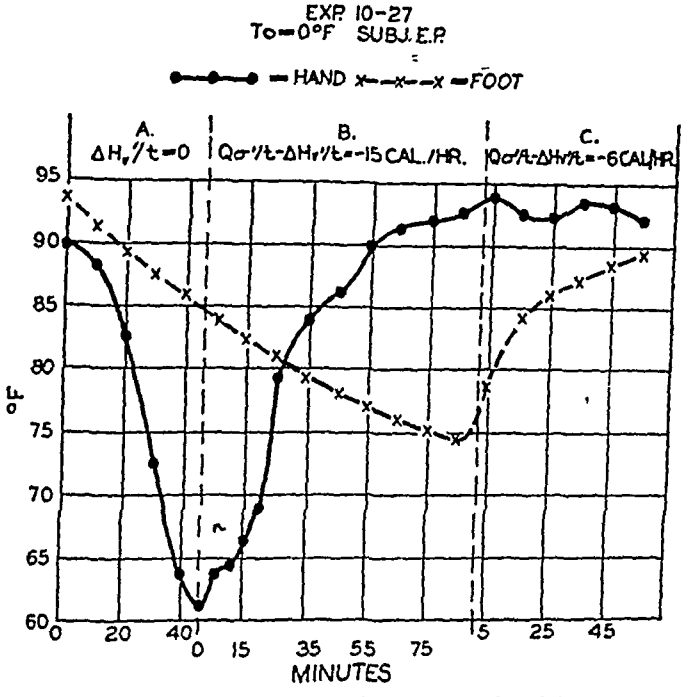

Fig. 2. EFFECT OF REWARMING the cooled body on hand and foot temperatures.

8-27, and *9-17*, table 1). When the net heat loss from the system was large, both the hands and feet cooled; but the rate of cooling of the hands was greater than that of the feet (*exper. 7-15*, figs. 1, 2). Since, in this circumstance, the blood vessels of both the hands and feet are constricted, the slower fall of foot temperature is the result of the heavier insulation of the footgear, and the smaller surface area per mass of the foot.

During the latter part of an experiment (*8-5*) at 0° F. there was a small net heat loss which resulted in a fall of average foot temperature but not of average hand temperature. In period A (see table 1), a slight excess of heat was furnished; average hand temperature was maintained at about 90° F. and average foot temperature at about 82° F. In periods B and C, the heat supply was reduced so that deficits were 17 and 21 Cal/hr., respectively (less

than 10% of $Q\sigma'/l$). Average hand temperature continued above 90° F., but average foot temperature fell to 65° F. in about $3\frac{1}{2}$ hours.

When the body was heated after the extremities had been allowed to become cold, foot temperature continued to drop until the hands had completely rewarmed. Figure 2 shows an 85-minute lag between the initial rise in hand and foot temperatures. Only a very small part of this lag can be attributed to the

TABLE 1. SUMMARY OF EXPERIMENTS SHOWING EFFECT OF VARIATION OF HEAT SUPPLIED TO BODY

EXPER.	T_o (°F.)	$\frac{Q\sigma'/l - \Delta H_v'/l}{\text{(CAL/HR.)}}$	% DIFF.	TEMPERATURE RESPONSES OF HANDS AND FEET
7-15	−1	−72	−41	Hand temperature fell to 60°F. in 90 min. Foot temperature fell to 75°F. in 90 min.
8-7A	+3	−3	−1	Hand and foot temperature kept above 90°F.
8-7B	+2	−30	−15	Hand temperature maintained above 85°F. Gradual fall of foot temperature to 75°F. in 2 hrs.
7-29A	+1	−26	−13	Hand temperature fell to 60°F. in 60 min. Slow fall of foot temperature to 79°F.
7-29B	+1	−41	−20	Electrical heating of hands necessary. Gradual fall of foot temperature to 60°F. in 2½ hrs.
8-5A	+2	+20	+10	Hand temperature kept at 90°F., foot temperature, above 80°F.
10-21	+4	+10	+6	Hand and foot temperature kept above 85°F.
7-31	+4	+25	+11	Hand and foot temperature kept at approx. 87°F.
8-14	−17	+42	+16	Hand and foot temperature kept at approx. 85°F.
8-25	−19	+28	+11	Hand temperature kept at about 80°F., foot temperature, at about 82°F.
8-27A	−20	−52	−20	Hand temperature fell to 64°F. in 25 min.; foot temperature, to 78°F.
8-27B	−21	+10	+5	Hand temperature rose to 90°F., foot temperature kept at about 70°F.
9-9	−31	+33	+12	Hand temperature kept above 90°F., foot temperature, above 85°F.
9-10	−31	+19	+7	Hand and foot temperature kept between 84–90°F.
9-17	−31	+32	+12	Hand temperature kept above 90°F., foot temperature, about 70°F.
11-4	−31	+13	+5	Hand and foot temperature kept above 85°F.

greater heat capacity of the footgear: about one Calorie is required to rewarm the boot.

Effect of a Sudden Increase in Cold Stimulus Applied to the Hand. The effect of a sudden increase in the cold stimulus applied to the hand when the body was warm was observed in 10 experiments by removing one glove within a cold room, and in 9 more by inserting a bare hand into a cold box while the body was heated. The former are summarized in table 2. In most of these, the assembly received slightly more heat (10 to 38 Cal/hr.) than was calculated as being lost. In several, a thin rayon insert was substituted for the glove,

but in others the hand was bare. There were three experiments (nos. *8-25*, *9-10*, and *9-17* first period) in which the temperature of the hand fell rapidly requiring termination within 20 minutes. However, in subsequent trials using the same subjects, hand temperatures were maintained at or above 70° F. In *experiments 10-27* and *10-30* hands stayed warm in spite of a heat deficit of 8 and 20 Cal/hr.

Hand temperature fell to about 55° F. when the glove was removed in *experiments 10-28*, and was maintained there for 60 minutes. It was then discovered that the tube supplying air to the trunk was disconnected. After it

TABLE 2. SUMMARY OF EXPERIMENTS IN WHICH ONE GLOVE WAS REMOVED IN A COLD ROOM

EXPER.	T_o (°F.)	INSULATION	$\frac{Q\sigma'/l - \Delta H_v'/l}{(CAL/HR.)}$	EFFECT UPON AVERAGE HAND TEMPERATURE
10-21	0	*Hand bare*	+10	Initial fall to 73° F., then rise to 85° F. for 50 min.
10-27	0	Hand bare	−8	*Maintained between 70 and 80° F. for 95 min.*
10-28	0	*Hand bare*	—	*Fell to 55° F. for 60 min. but rose to 78° F. when heat to body increased.*
8-25	−20	Hand bare	+38	Rapid fall, hand painfully cold after min.
8-27	−20	*Rayon insert*	+10	*Fell to 60° F. in 15 min., then rose to above 70° F. for 30 min.*
9-9	−30	Rayon insert	+33	Maintained at about 85° F. for 50 min.
9-10	−30	Rayon insert	+19	*Fell within 10 min. to 40 and 47° F., respectively on two trials, but each time returned to above 85° F. when glove replaced.*
9-17	−30	*Rayon insert*	+32	*Fell on first trial to 50° F. within 20 min. Maintained between 70 and 80° F. for 50 min. on second trial.*
10-30	−30	Hand bare	−20	Maintained between 77 and 84° F. for 60 min.
11-4	−30	Hand bare	+13	Maintained at about 70° F. for 60 min.

was reconnected, hand temperature rose to 78° F. in 22 minutes. In the remaining experiments, the temperature of the exposed hand was maintained above 70° F. for an experimental period of from 45 to 95 minutes. Two experiments at −30° F. are illustrated in figure 3. In both instances the temperature of the bare hand was maintained above 70° F. for 60 minutes, and the exposure probably could have continued.

Data from the experiments in which the bare hand was placed in a cold box are presented in table 3. The temperature of the box air, T_a, was 0° F. in the first three experiments, and −30° F. in the others. Both average hand and fingertip temperatures were measured, but only the temperature of the tip of the fifth finger, T_{f5}, is given in the table. In that part of the experiment in

which the hand rapidly became cold, T_{f6} was usually about 10° F. below average hand temperature at the end of the exposure. When the body was heated and hand temperature maintained at comfort level, T_{f6} was generally about 5° F. higher than average hand temperature. However, on occasions, the difference was as little as 1 or 2° F., or as much as 10° F. The time given in the table is minutes of exposure. The temperature given at zero minutes was measured just before the hand was placed in the box.

With the box at 0° F. and the body cooled, finger temperatures fell to about 40° F., and the hand was painfully cold, within six minutes. With the box at −30° F., the duration of exposure with the body cooled was reduced to two to four minutes. (In one experiment in which the body was only slightly chilled the duration of exposure was 13 minutes). In contrast, when the body

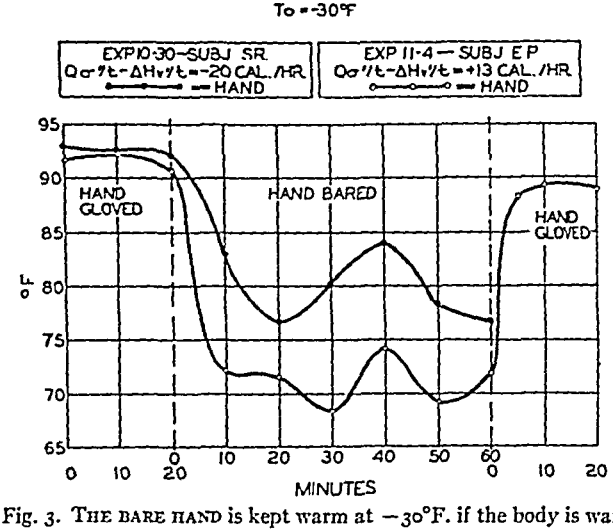

Fig. 3. THE BARE HAND is kept warm at −30°F. if the body is warm.

was heated in the three experiments at 0° F., finger tip temperatures were sustained above 70° F. throughout an experimental period of 40 to 60 minutes. When the hand was placed in the box at −30° F. with the body heated, finger tip temperatures were maintained above 70° F. for 50 to 60 minutes in five experiments. In a first trial upon S.F., the hand had to be removed from the box after 10 minutes. In a second trial, begun a few minutes later, finger tip temperatures were maintained at comfort level for fifty minutes. At the end of that time, however, the hand again became cold. In an experiment upon H.S., skin temperatures were maintained for 30 minutes and then suddenly began to fall. In the remaining experiments there was nothing to indicate that the exposure could not have been continued. The experiment upon G.H. is worthy of comment in that at −30° F. finger temperature rose to 98° F. and

was maintained at that level. As the hand was withdrawn from the box, it was noted to be actively sweating. In general, the hand remained comfortable in the box at −30° F. whenever finger-tip temperatures were above 70° F.; but occasionally a subject complained of coldness of the skin overlying the knuckles or along the sides of the hand.

DISCUSSION

These experiments clearly demonstrate that, at least to −30° F., regulation of the blood flow to the hands and feet is primarily determined by the thermal state of the body as a whole. Vasoconstriction need not occur provided the body does not have to conserve heat. Under conditions comparable to these experiments, artificial heating of the hands and feet is unnecessary; they will be adequately heated by their blood supply. However, the supply of a quantity of

TABLE 3. SUMMARY OF COLD BOX EXPERIMENTS PERIOD OF BODY HEATING

SUBJECT	T_a, °F.	EXPOSURE TIME (MIN.) 0	10	20	30	40	50	60	SUBJECT	T_a, °F.	EXPOSURE TIME (MIN.) 0	10	20	30	40	50	60
		T_{fi}, °F.									T_{fi}, °F.						
S.R.	0	96	82	82	78	74			S.R.	−30	—	75	76	72	77	77	78
H.S.	0	95	87	87	84	80	84		H.S.	−30	93	75	72	67			
J.H.	0	93	79	73	79	76	75	82	G.H.	−30	96	88	81	95	98	98	98
S.F.	−30	95	53						D.L.	−30	94	87	83	79	80	74	75
S.F.	−30	96	77	79	79	81	75		R.S.	−30	97	84	86	87	86	87	

heat which is large but still not equal to that being lost was usually as ineffective in preventing vasoconstriction and subsequent cooling as the failure to supply any heat at all. Thus, the hands and feet became cold in those experiments in which there was a net heat loss of greater than about 15 per cent. This observation is confirmed by the example of the electrically heated flying suit, in which failure of the power supply to a glove or boot insert will result in rapid cooling of the affected extremity despite the considerable amount of heat being supplied to the rest of the body. It would appear that cooling of the extremities may be used as an indication in many conditions that the amount of heat available is insufficient, that is, that the body is attempting to conserve heat.

The experiments in which the extremities were rewarmed demonstrate that adequate heating of the body not only can prevent peripheral vasoconstriction, but often can reopen constricted vessels in cold extremities. After a fall to 55 to 60° F., hand temperature may return to control level in 20 to 50 minutes. No satisfactory explanation can be offered for the failure of the ex-

tremities to rewarm in one experiment. It emphasizes the need for further study. It would also be desirable to know if the extremities could be rewarmed by this method after they had been allowed to cool to temperatures just above freezing.

It is a common experience for the feet to feel cold while other body areas are comfortable. The data of Roth, Horton, and Sheard (10) demonstrate that the temperature of the toes is the first to drop when the nearly nude body starts to cool and the last to rise when it is warmed. The differences in the temperature response between the hands and feet in our experiments are in agreement with this observation. In the rewarming experiments, average foot temperatures continued to fall until hand temperatures had returned to normal.

That the temperature of the bare hand at −30° F. was sustained above 70° F. is striking evidence that the vasoconstrictive effect of severe cold is subordinate to the autonomic control of blood flow in the hand. This is not to say that the cold stimulus is without effect. Hand temperature invariably fell 5 to 25° F. when the glove was removed or the hand inserted into the cold box. The hand did not show the deepening of color and reddening, which is usually seen when skin is exposed to cold. The reason for the failure of the hand temperature to stabilize in three experiments in the cold room and in one cold box experiment is not known. In two of these experiments, the temperature of a finger on the opposite hand, the one which had remained gloved, also dropped sharply (from 88° F. to 65° F. in one experiment and from 90° F. to 58° F. in the other). It is our impression that tenseness or anxiety about the experimental procedure contributed to the vasoconstriction. That emotions of this nature may be accompanied by peripheral vasoconstriction is generally recognized. Of practical importance was the fact that replacement of the glove brought about a prompt return of hand temperature to comfort level. Increased air movement and contact with solids have not been considered; these factors would increase the rate of heat removal from the hand.

The experiments in which the glove was removed in the cold room differed from the cold box experiments in one important respect. In the former there was little or no heat excess supplied to the body; in the latter, there was definite overheating and considerable sweating. The fact that hand temperatures were sustained in both circumstances indicates that overheating is not essential to sustain blood flow through the non-heated extremity at temperatures down to −30° F.

The purport of these results is that the temperature of the extremities can be made nearly independent of the ambient temperature and of insulation over a wide range; and dependent primarily upon the thermal state of the body as a whole. The practical implications are many. For example, most electrically

heated clothing supplies large amounts of heat to the hands and feet. Relatively more of the heat is wasted from these areas than from the trunk and limbs because of the lesser insulation of the gloves and boots, and the position of the heating elements. Transfer of this heat to the trunk and limbs might make such clothing more efficient, cheaper to manufacture, and more durable. The importance of keeping the whole body warm in the prevention of frostbite is readily apparent. These results also emphasize the importance of supplying heat to the whole body, rather than to the affected part alone, in the relief of the vasospasm associated with most peripheral vascular disorders.

Attempts to induce rapid adaptations or modifications of human physiology to meet high environmental stresses have been generally unsuccessful. The observation that extremity temperature can be made relatively independent of the environmental temperature does offer the possibility of practical control of a physiological response. Many problems, theoretical and practical, remain to be solved. Among the more important are *a*) the analysis of the mechanisms; *b*) the extent of individual variation; *c*) the relative importance of thermal level as compared with the rate and direction of thermal state change; and *d*) the establishment of the lower limits of control.

CONCLUSIONS

The regulation of blood flow to the extremities at low ambient temperatures is primarily determined by the thermal state of the body as a whole. Experiments in which the bare hand was exposed to temperatures of 0 to −30° F. clearly demonstrate that the vasoconstrictive effect of severe cold is subordinate to the autonomic control of blood flow in the extremities, since hand skin temperature could be sustained above 70° F.

Therefore, the temperature of the extremities can be made nearly independent of the ambient temperature and of insulation, over a wide temperature range; and dependent primarily upon the thermal state of the rest of the body. Under conditions comparable to these experiments, artificial application of heat to the extremities is unnecessary for their comfort.

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Quantitation of the Output of Individual Sweat Glands and Their Response to Stimulation[1]

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VARIATIONS IN SWEATING RATES on different parts of the body have been observed frequently (1–4) and variations in the numerical distribution of sweat glands over the surface of the body are well known (5, 6). Quantitative information concerning the output of individual glands is lacking, yet such information holds significance in attaining a better understanding of how the functional units operate in sweating responses. Among the reasons that the precise nature of the sweating response remains obscure is that it has not been possible to differentiate between those responses in which greater numbers of glands are activated from those in which glands already functioning simply react with greater frequency or intensity. Randall (7) suggested the inference based upon experience with the iodine-starch-paper technique that the first sweating response of a large area of the body to heat was an increase in the number of active glands, each discharging a relatively small amount of sweat. As the heating continued, increasing size of the sweat spots on the starch paper gave qualitative indications of a secondary increase in sweating based upon greater output by the individual glands.

Simultaneous observations upon the number of active glands and the quantitative output of sweat from the same area should furnish a more critical evaluation of the manner in which the sweating mechanism responds to stimulation. Accordingly, areas were chosen in which the numerical distribution was found to be quite constant, and this area subdivided so that sweat could be collected from one part while continuous counts were made on an immediately adjacent part. Estimations could then be made of the output of what might be called an 'average' or 'typical' sweat gland for that particular area.

METHODS

For the collection of sweat, small metal capsules were prepared as illustrated in figure 1. In addition to the blotter disc illustrated, a second disc of absorbent paper was cut to fit precisely into the capsule and the complete unit covered by a small glass plate. This unit could be heated in an oven and stored

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in a $CaCl_2$ desiccator flask. Immediately before use, the capsule, including the glass plate and discs of absorbent paper were weighed on a precision chain-o-matic balance. The glass cover and outer disc of absorbent paper were quickly removed and stored in the desiccator while the capsule was inverted and taped firmly over the test area. Sweat counts, using a method previously described (6) were started immediately. At the end of a suitable test period (usually about 10 minutes) the capsule was removed and the blotter disc from the desiccator applied over the test area to pick up any unabsorbed sweat. The change in weight of the capsule and absorbent paper was carefully observed. Blank capsules were run simultaneously with each set of experiments in order to correct for errors induced by variations in environmental temperature and humidity.

Checks to determine the efficiency of this technique for the quantitative collection of water were made by placing the capsules over a small weighed

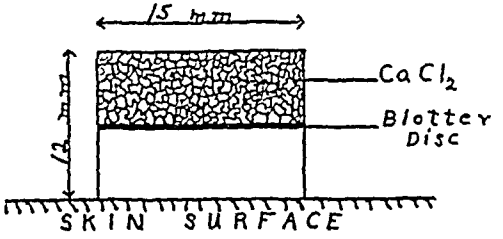

Fig. 1. SMALL METAL CAPSULE shown inverted over skin during collection of sweat. An additional blotter disc and small glass cover are stored in $CaCl_2$ desiccator during period of collection, the blotter disc then being applied over test area to take up any moisture not absorbed by the capsule.

droplet of water for comparable periods of time, and it was found that an average of 96 per cent of the water was collected. Comparison of our data on sweating with that derived from the accurate method of Burch and Sodeman indicates reasonable correspondence. The consistently higher values in our data are undoubtedly explained by the consistently higher wet and dry bulb temperatures in our experiments.

RESULTS

It has been shown that while a subject is resting quietly in a warm environment, normal sweating responses consist of cyclic discharges by larger and smaller numbers of sweat glands (7). During several successive cycles, certain glands may be repetitively active while others are only occasionally active. That is, there may be considerable alternation among the glands of a given region during any one or any series of cycles. The expression of output in terms of mg/min. therefore may give a somewhat misleading impression of the manner of function of the individual glands, but technical limitations make more precise expression difficult at the present time. Although direct cannulation of the sweat pores by fine capillary tubing introduces a relatively large mechanical obstacle to the outflow of sweat, this technique in the hands of Takahara

(as described by Kuno, 1) has demonstrated that from .003 to .005 mg. of fluid is discharged during a period of 12 to 30 seconds when a palmar sweat gland becomes active. It should be recognized therefore that the minute output of many glands in a given area may vary considerably from the values calculated for the 'average' gland.

Simultaneously recorded cycles of sweating from three areas of the normally sweating upper extremity are shown in figure 2. Also shown are the amounts of secretion collected on each of the three areas during this period of recording. It is immediately evident in this experiment that sweating progressively

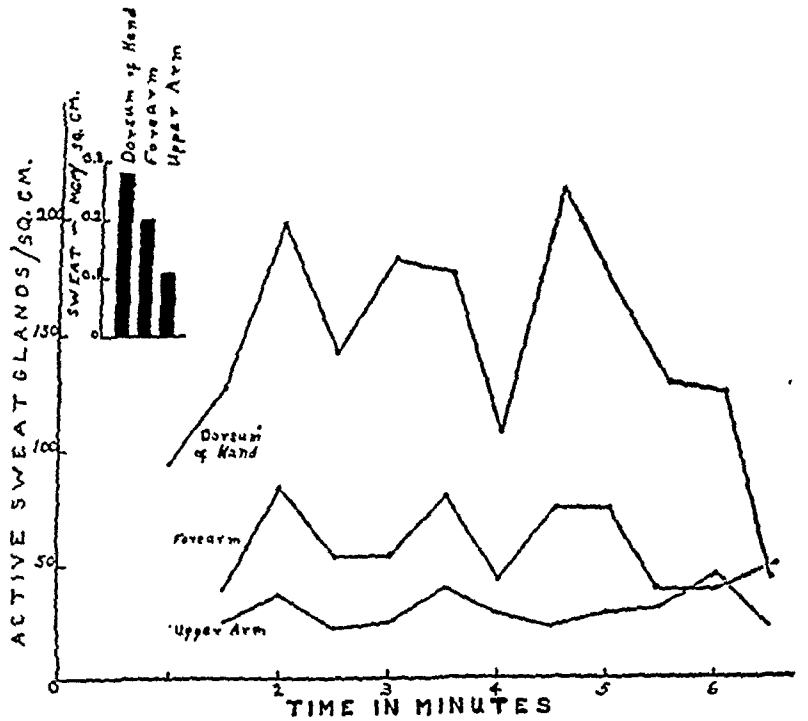

Fig. 2. GRAPH ILLUSTRATING SIMULTANEOUS RECORDING of sweat spots from three areas of the upper extremity, together with a representation of the quantitative collection of sweat during this period.

decreased from the distal to the more proximal regions of the arm, differences being prominent both in the number of functional glands and in the quantity of sweat secreted. It should be noted here that our experience was consistent concerning this gradient in sweating on the upper extremities, and therefore represents a failure to confirm the report of Weiner on this point. Palmar sweating was omitted from these comparisons because psychic factors limit the consistency of results in this area and because the palmar sweat glands are known to be of lesser importance in thermal sweating. It has been our experience, however, that the palmar surfaces are capable of sweat outputs considerably in excess of all other surfaces of the arm.

Calculations derived from the expression:

$$\frac{\text{mg. sweat secreted/sq.cm/min.}}{\text{av. number functional glands/sq.cm/min.}}$$

show the average output of the individual glands of the upper arm and forearm in figure 2 to be .0033 and .0035 mg/min. respectively. Similar calculations from data on the dorsum of the hand, however, show that the number of active glands is disproportionately high as compared with the total sweat output, so that the output of individual glands in this area was only .0020 mg/min.

Similar observations were made on the lower extremities and are summarized in the comparative data in table 1. During these experiments dry bulb temperatures were consistently high (82 to 92° F.) while the relative humidity showed variation (35 to 80 per cent) from experiment to experiment but was generally high. The data show that the output of the average gland is comparable on the arms and legs, and that although it is comparable on the dorsal surfaces of the hand and foot it is significantly lower on these areas than on the arm and leg. These quantitative calculations are confirmed qualitatively by the appearance of the sweat spots on the starch paper records. The sweat spots on the dorsal surfaces of the hand and foot are small but relatively numerous whereas the spots on the arm and leg are larger but less numerous.

Whether these differences in output are due to morphological or functional variations is not known, but similar studies carried out under conditions of maximal or nearly maximal sweating should give indication as to which of these factors limits the output. Therefore it was decided to compare the outputs of these glands when directly stimulated by cholinergic drugs. Mecholyl (acetyl-beta-methylcholine)[2] was forced into the skin by the process of ion transfer at a current density of approximately 0.07 ma/sq.cm. The results of these experiments are summarized in table 1. It is apparent that increases of 50 to 150 per cent occurred both in number of functional glands and in sweat output. The same gradient in numbers of glands and in output of sweat is observed from the dorsum of the hand to the upper arm but this difference in distribution and output is not as apparent on the lower extremity. Attention is directed to the particularly large output of the glands on the leg, since this may contribute very significantly to the large part played by this area in evaporative heat losses. Calculations of output for the individual glands, however, show much the same relative differences between the dorsal surfaces of the hand and foot and the arm and leg. It is perhaps significant here that even the higher extremes in the range of values on the hand and foot do not overlap significantly the lower extremes in the range of values on the arm and leg. Although it must be

[2] Mecholyl furnished through courtesy of Mr. A. W. Veazey of Merck and Company.

admitted that this evidence is indirect, it appears that morphological limitations are the important factors in limiting the secretion per minute by the glands on different regions of the body. It is well known, of course, that such morphological differences do exist as illustrated by the histological comparisons of Way and Memmesheimer (8). These authors found variations in diameters of so-called small, medium and large glands from 100 microns to 1 mm. or more.

In order to study the responses of the sweating mechanism to such normal

TABLE 1

AREA	NORMAL SWEATING IN WARM ENVIRONMENT			SWEATING DURING MILD EXERCISE			SWEATING AFTER MECHOLYL		
	Sweat Collected	No. Active Sweat Glands	Av. Output/ Gland	Sweat Collected	No. Active Sweat Glands	Av. Output/ Gland	Sweat Collected	No. Active Sweat Glands	Av. Output/ Gland
	mg/sq. cm./min.	*per sq. cm.*	*mg/min.*	*mg/sq. cm./min.*	*per sq. cm.*	*mg/min.*	*mg/sq. cm./min.*	*per sq. cm.*	*mg/min.*
Upper arm	.104 (.01–.188)	27 (10–41)	.0037 (.0019–.0055)	.183 (.05–.32)	53 (23–85)	.0033 (.001–.005)	.558 (.22–1.2)	83 (49–131)	.0067 (.004–.009)
Forearm	.176 (.04–.25)	41 (5–57)	.0043 (.002–.013)	.253 (.13–.40)	69 (27–110)	.0037 (.001–.005)	.565 (.3–.75)	99 (44–130)	.0057 (.004–.008)
Dorsum hand	.306 (.04–.37)	99 (5–150)	.0031 (.001–.008)	.322 (.09–.71)	153 (23–235)	.0021 (.001–.004)	.970 (.60–1.2)	220 (130–270)	.0044 (.002–.005)
Thigh	.150 (.05–.20)	38 (8–66)	.0040 (.001–.006)				.577 (.16–1.2)	81 (20–178)	.0071 (.004–.008)
Leg	.195 (.14–.22)	47 (6–82)	.0042 (.002–.009)				.785 (.30–1.6)	73 (60–125)	.0108 (.006–.017)
Dorsum foot	.193 (.18–.22)	93 (42–141)	.0021 (.001–.005)				.566 (.47–.68)	182 (178–185)	.0031 (.002–.0037)

Bold face values represent average sweat outputs or average numbers of glands. Values enclosed in parentheses represent the range of values.

requirements for increased evaporative heat loss as occurs in mild exercise, a simple weight-lifting device was constructed in such a way that the subject could do a small, measured amount of work with his feet and legs while sweating responses were studied on the upper extremities. These studies were carried out in a room sufficiently warm that sweating could be initiated with relatively little muscular exertion. Under such circumstances the increase in sweat gland activity is evident on all surfaces of the arm (table 1). There occurs a prompt increase in number of functioning glands together with an almost proportional increase in sweat collected from the area. This is interpreted to mean that under such circumstances the increase in sweat on the upper extremity is almost

entirely due to an increase in number of glands with little or no increase in output by the separate glands. Indeed, in most of the observations there was evidence that the calculated output per gland was slightly reduced.

The interesting question immediately arises as to how, in the presence of active sweating in a given area, still greater sweating may be brought about. It is well known that increased sweating follows exposure of the body to high environmental temperatures or partial immersion in hot water baths. The outbreak of sweat is generalized over the body surface and is more profuse with longer exposures or higher environmental temperatures. On the basis of qualitative experiments carried out in hot water bath experiments, it was suggested

TABLE 2

FOREARM	TIME	MG.SW/CM²/MIN.	AV. NO. SW. SPOTS	AV. OUTPUT/GLAND
Subject *RA*	0–10th min.	.085	31	.0027—control sweating
	In water bath (44° C.) at end of 15th minute			
	20th–25th min.	.343	81	.0042—initial response to heating
	35th–38th min.	1.713	175	.0098—delayed response to heating
	Bath temperature gradually elevated from 25° to 42° C.			
Subject *CA*		.612	112	.0054—initial response to heating
		1.082	115	.0094—progressive response
		1.342	104	.0129—delayed response

Sweating responses to exposure of body to heat by partial immersion in hot water bath.

that the first response of the sweating mechanism is to increase the number of functioning glands, but if the resultant increase in heat loss is insufficient to meet demands of body temperature regulation, the individual glands are able to increase output. Table 2 illustrates two types of such responses on the forearm. At the end of a preliminary control period in a warm room (0 to 10 min. in the table) subject *RA* sat with legs and thighs immersed in a hot water bath (44–45° C.). Sweating was immediately diminished for a period of two and one half minutes, after which a large number of small sweat spots appeared on the starch paper records. This preliminary inhibition of sweating was observed several times on both forearm and palmar surfaces. It apparently represents an inhibitory reaction on the part of the sweating mechanism to such massive sensory discharges from the cutaneous receptors. Following the preliminary inhibition a sample of sweat was collected (20th to 25th minute in the table) together with sweat pore counts. An increase, both in number of functional glands and in total sweat output, was observed. Calculation of the output of

the individual gland during this period indicated an increase of approximately 50 per cent whereas there was a simultaneous increase of about 165 per cent in the number of functional glands. As the exposure continued, the total output of sweat showed further marked increase. During this period, while the number of glands showed further increase of about 115 per cent, the calculated output per gland showed an additional increase of about 135 per cent. Thus it appears that there occurred both an increase in number of glands and in output per gland during both the initial response and during the delayed response, but the initial response was predominately one of numbers of glands while the delayed response showed some predominance in output per gland.

In a second type of response where relatively high secretory levels were evident at the beginning of the exposure (both in number of active glands and in quantity of sweat secreted), continued exposure to the high bath temperature induced further increase of sweat output with no further increase in numbers of functional glands (*subject CA*, table 2). One might safely assume that approximately the maximum number of functional glands in the area were active. In this type of response the increase in total volume of sweat output therefore appears to be related predominately to an increased output by glands which are already functioning.

DISCUSSION

This method of estimating individual gland output admittedly neglects the fluid loss from the test area by simple diffusion, together with possible fluid leakage through the walls of the sweat ducts in the stratum corneum. As yet we have not been able to ascertain precisely how large a fraction of the total secretion this represents. Since estimation of the so-called 'insensible perspiration' as found in the literature may or may not include participation of hitherto undetected functioning sweat glands, it is difficult to make appropriate corrections for this avenue of fluid loss. According to Kuno, physical passage of water through the epidermis does occur, but except for palmar and plantar surfaces its rate is small and fairly uniform over the body surface. Burch and Winsor (9) have shown that water loss by diffusion through dead skin and through non-sweating living skin is approximately 0.1 mg/sq.cm/min. on the epigastric surface. If these figures could be transferred directly to the skin of the arm and leg, it is evident that the control values in our data would be necessarily lower. In the complete absence of sweat spots on these surfaces however, we have not observed losses attributable to diffusion alone as high as those indicated in the experiments of Burch and Winsor. There may be different rates of loss by diffusion from different surfaces, particularly from the palmar, plantar, and forehead regions. Our data in these studies however are incomplete at the present time.

The experiments reported in this paper suggest that the maximum minute

output of an individual sweat gland is considerably greater than that which may be observed in the usual moderate sweating responses. It is also apparent that the sweating mechanism may respond to additional needs for evaporative heat loss by increases in the number of functioning glands, in increased output per gland or in a combination of these two responses. It is believed that the initial response is usually one of increased numbers of actively secreting glands. Since the sweat glands on the arm (and probably those on other body surfaces as well) normally discharge periodically rather than continuously, the increase in glandular output may be explained by assuming more frequent discharges per minute or an absolute increase in quantity of sweat poured onto the skin surface during each discharge. Either response would result in an increase in minute output per gland.

It is not known precisely how the nervous system controls the secretory activity of the sweat glands. Additional glands are undoubtedly brought into action by the participation of larger numbers of sudomotor fibers, and this might well be the initial response of the heat regulatory mechanism in meeting demands for greater heat dissipation. Then if this response proves inadequate to meet the demands for heat loss, one might imagine an increase in frequency of impulses over these same pathways resulting in more frequent discharges by the innervated sweat glands. Such reasoning might presuppose that any single discharge of sweat is more or less fixed and constant for a given gland, and any increase in minute output be related to variations in frequencies of discharge. It remans possible however that a given gland and duct lumen may be more completely emptied under conditions of greater stimulation and thus show larger quantity of sweat poured out onto the surface during a single discharge. There is some evidence that the secretory portions of the glands are supplied with nerve endings, and the production of greater quantities of secretion coincident with excessive stimulation is therefore plausible.

SUMMARY

A technique for the estimation of output of individual sweat glands is described and discussed.

Calculations of output of sweat glands on the arm and leg show greater average values on these areas than on the dorsal surfaces of the hand and foot. Similar differences were observed when the glands were stimulated by the introduction of mecholyl into the skin by ion transfer.

The excitation of the sweating mechanism by mild muscular exercise is marked chiefly by an increase in number of functional sweat glands with little or no increase in output per gland. Upon more severe stimulation such as accompanies partial immersion in hot water, an increased number of functional glands may be supplemented by increased output per gland in a given period of time. The possible ways in which this could be accomplished are discussed.

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Venous Pressure and Cutaneous Reactive Hyperemia in Exhausting Exercise and Certain Other Circulatory Stresses[1]

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IT IS DIFFICULT to assess the functional significance of the elevations of venous pressure reported in patients with cardiac failure, at rest or during exercise, partly because published results do not agree concerning the effects of exercise on the venous pressure of normal subjects (1–4), and partly because the relations between venous pressure, compensatory vasoconstriction, tachycardia and pulmonary ventilation have not been studied together in normal subjects. It has been suggested on the basis of experiments on dogs (5) that a sudden rise of systemic venous pressure may considerably reduce 'effective' and absolute blood volume respectively, *a*) because the distended veins and venules may then contain a greater fraction of the circulating blood than usual and *b*) because filtration is increased, and absorption decreased, over large areas of capillary bed. Loss of fluid from the blood stream by filtration from all areas with high venous pressure will be cumulative and added to the well-known filtration which occurs in exercising muscle itself (6). The collective effect on blood volume may be considerable, to judge from calculations based on earlier plethysmographic observations (5). Moreover, an elevation of venous pressure by as little as 5 mm. H_2O produces definite increase of capillary filtration in the perfused limb (7) and, other factors remaining constant, the balance between filtration and absorption is 5 to 10 times more sensitive to changes of venous pressure than to changes of arterial pressure. Hence, any sudden rise of venous pressure may have considerable effect on available blood volume.

In normal subjects renal blood flow decreases during moderate exercise (8, 9). While a brief neurogenic vasoconstriction in the digits early in exercise has been described (10), nothing is known concerning the reactions of the cutaneous vessels late in exhausting exercise, or in areas other than the digits.

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[2] Alexander McPhedran Fellow, 1946–47, from the Department of Medicine, University of Toronto.

[3] Student Research Fellow, Life Insurance Medical Research Fund, 1946–47.

This paper describes *a*) the effects of graded treadmill exercise on peripheral venous pressure of normal subjects, *b*) the appearance of vasoconstriction in the skin of the forearm (measured by reactive hyperemia) as exhaustion approached and *c*) the relations of these changes to the increased heart rate and pulmonary ventilation of exercise. In contrast, certain less acute circulatory stresses were accompanied by less or no change of reactive hyperemia in the skin of the forearm.

METHODS

Normal, fasting (8 to 12 hours) male subjects, ranging in age from 20 to 45 years, and clothed only in shorts were given graded exercise on a motor-driven treadmill for consecutive 10-minute periods at speeds ranging from 1.5 to 3.0 miles per hour and grades varying from 0 to 10°. Room temperature ranged from 24° to 27° C.

Venous pressure (mm. saline) was measured directly in a vein of the left forearm or hand using heparinized saline. The zero point of the manometer was set at the level of the xiphoid process, and the chosen vein was also kept in this plane by raising or lowering an adjustable support on which the forearm and hand rested. When walking on a grade, subjects tend to lean forward. Hence, to compensate for the downward shift of the heart, several lines were drawn from the xiphoid which were parallel to the floor when the subject was exercising at various grades. At each grade the zero point of the manometer could then be shifted to correct for this change in posture. With this precaution the venous pressure, as measured in the arm, did not change with mere tilting of the body.

Local cutaneous reactive hyperemia (11) was measured in the middle of the volar surface of the elevated right forearm according to the modified technique of Greenwood *et al.* (12) using a weighted plastic ring to occlude the skin vessels. 'Threshold' is the least duration of application of the ring (in seconds) required to produce the complete hyperemic circle having a width equal to the surface of the ring. 'Clearing time' is the time (in seconds) for the complete disappearance of that reactive hyperemia which has been produced by an occlusion of threshold duration. The forearm was elevated to exclude artefacts from changes in venous pressure. Temperature and venous pressure remaining constant, an increase in threshold and clearing time indicates an increase in the tone of the minute vessels of the skin (12) and a decrease in threshold and clearing time, a decrease in tone.

Skin temperatures were recorded every 10 seconds from *a*) the forehead, *b*) the forearm near the site where reactive hyperemia was measured, and *c*) the pulp of a finger of the left hand. The soldered iron-constantan junctions were secured to the skin by collodion. To lessen the effect of evaporative cooling, the thermal junctions were covered by a piece of thin rubber dam ranging

in size from 1 cm. square on the digits to 4 cm. square on the forehead and forearm. Rectal temperature was recorded continuously by a Foxboro resistance thermometer.

In some of the experiments the respiratory minute volume was measured by passing the expired air through a gas meter, while the respiratory rate was

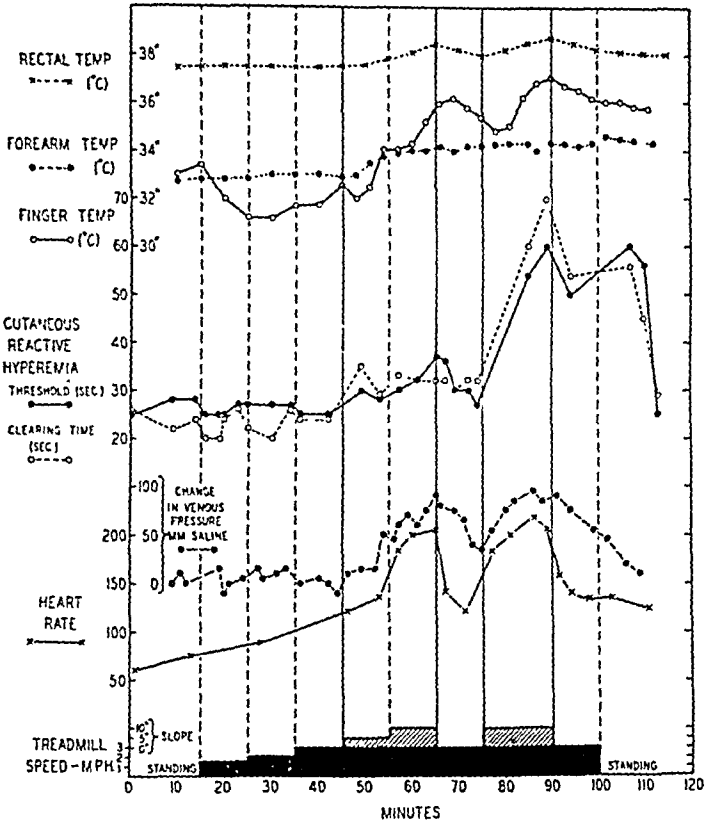

Fig. 1. CHART SHOWING REPRESENTATIVE TREADMILL EXPERIMENT; effects of exhausting work on venous pressure, heart rate, cutaneous reactive hyperemia, skin and rectal temperatures.

recorded on a kymograph by a float on a manometer placed in the expiratory line.

OBSERVATIONS

The results of a representative experiment are charted in figure 1. After a 30-minute preliminary rest period in the recumbent position, control observations were recorded with the subject standing in position on the treadmill. The subject then walked for consecutive 10-minute periods (see bottom fig. 1) at 1.5, 2.0, and 3.0 miles per hour on the level, followed by 3.0 miles per hour first at a 5° grade and then at 10°. In order to differentiate more clearly between

the results due to intensity of work and those due to its duration, the subject was returned to the level at 3.0 miles per hour for 10 minutes and then finally exercised at 3.0 miles per hour and 10° until the approach of exhaustion. The last 10-minute work period at 3.0 miles per hour on the level was included to reduce the incidence of postexercise syncope. Observations were ended with a 10- to 30-minute period during which the subject stood at ease on the treadmill.

In general, heart rate increased slightly as soon as walking began, but venous pressure, and the threshold and clearing times of reactive hyperemia increased very little until the subject began to walk on the grade. Heart rate and venous pressure generally rose about equally during the first and second

TABLE 1. EFFECT OF GRADED EXERCISE ON PERIPHERAL VENOUS PRESSURE

SUBJECT	DIFFERENCE (MM. SALINE) FROM VENOUS PRESSURE WHEN STANDING AT REST									
	Standing before exercise	1.5 M.P.H. level	2.0 M.P.H. level	3.0 M.P.H. level	3.0 M.P.H. 5°	3.0 M.P.H. 10°	3.0 M.P.H. level (2nd per.)	3.0 M.P.H. 10° (2nd per.)	3.0 M.P.H. level (3rd per.)	Standring after exercise
W.G.	0	−10	−10	−20	+25	+50	+15	+80	+25	0
J.S.	0	−5	−5	0	+15	+75	+30	+110 (35 min.)	+70	+40
L.H.S.	0	−5	0	+15	+20	+60	+40	+95 (15 min.)	+65	+20
R.K.	0	+5	+20	0	+20	+75	+35	+85 (15 min.)	+55	+15
R.W.	0	−5	+10	+20	+55	+90	+65	+80 (13 min.)	+45	+10
B.M.	0	−30	−25	−20	+45	+85	+25	+100	+15	0
Average change in venous pressure	0	−10	−2	−1	+30	+73	+35	+91	+46	+14
Average heart rate (beats/min.)	75	73	83	93	125	181	110	200	121	103

periods of exercise on the grade. In contrast, reactive hyperemia changed moderately but definitely during the first bout, but markedly during the second bout, as exhaustion approached. These effects will now be described in series more quantitatively.

Effect of Graded Exercise on Venous Pressure. In order to compare changes of venous pressure in a series of subjects, the figures have been expressed in terms of deviation from baseline values of venous pressure (mm. saline) observed during quiet standing. Table 1 summarizes the results obtained on 6 subjects. The figures refer to the level of venous pressure at the end of each 10-minute period (or at exhaustion) as compared to the resting value.

With the onset of mild exercise (1.5 miles per hour on the level) venous

pressure did not change significantly from that observed during quiet standing, although the average figures do show a slight decrease. At 2.0 and 3.0 miles per hour on the level, the venous pressure remained quite close to resting values with a slight tendency to rise in some instances. The first significant and consistent rise in venous pressure occurred on the 5° grade at 3.0 miles per hour. This exercise, continued for 10 minutes, raised venous pressure by 15 to 55 mm. saline above the control value. Ten minutes' exercise at the same rate, but at a 10° grade elevated peripheral venous pressure by 50 to 90 mm., accompanied by distension of the visible neck veins. In 25 observations carried to exhaustion, venous pressure rose 80 to 100 mm. of saline above control values, except in two instances where it rose above 100 mm.

In agreement with Schneider and Collins (4) we found that the elevation of venous pressure was roughly proportional to the work intensity, and that the pressure did not drop abruptly at the end of exercise. Average venous pressure was also higher by 18 mm. saline during the second bout of 3 m.p.h. at 10° grade than during the first bout. After this latter period of severe exercise, the venous pressure fell slowly during the final 10 minutes at 3.0 miles per hour on the level and usually did not return to the resting value for 5 to 20 minutes, despite the pooling of blood in the lower extremities which accompanies quiet standing.

Effect of Graded Exercise on Localized Cutaneous Reactive Hyperemia. The appearance and persistence of cutaneous reactive hyperemia (and hence the tone of the minute vessels) usually remained within control limits until heavy work was performed. Threshold and clearing times usually varied in the same direction, but, in agreement with Greenwood *et al.* (12), we found that the clearing times showed greater random fluctuations than did threshold. Therefore, it was impossible to attribute as much significance to single estimations of clearing time as to single determinations of threshold.

A significant rise in threshold and clearing time occurred only on the 10° grade in most subjects (figs. 1 and 2, *A*, *B* and *C*). A more marked increase was usually observed at the approach of exhaustion during the second period at 10°. Hence, the tone of the cutaneous vessels did not increase significantly in normal, healthy subjects until late in exercise. Figure 2*D* illustrates a more striking response in an older subject in poorer physical condition. Three minutes at 10° taxed this subject to the limit of his endurance and produced a 200 per cent rise in threshold and nearly 400 per cent in clearing time.

The data on changes of reactive hyperemia during cumulative graded exercise are summarized in table 2. For purposes of comparison, three periods are considered. *Bout A* refers to the first period of exercise at 5° and 10° (total duration 20 min.). *Bout B* refers to that initial part of the second period (duration 15 min.) during which the work performed was equivalent in foot pounds to that previously done in *Bout A*. *Bout C* refers to the last part of the second

period at 10° (duration variable) from the end of *Bout B* until the observation had to be ended because of exhaustion. Thresholds and clearing times refer to

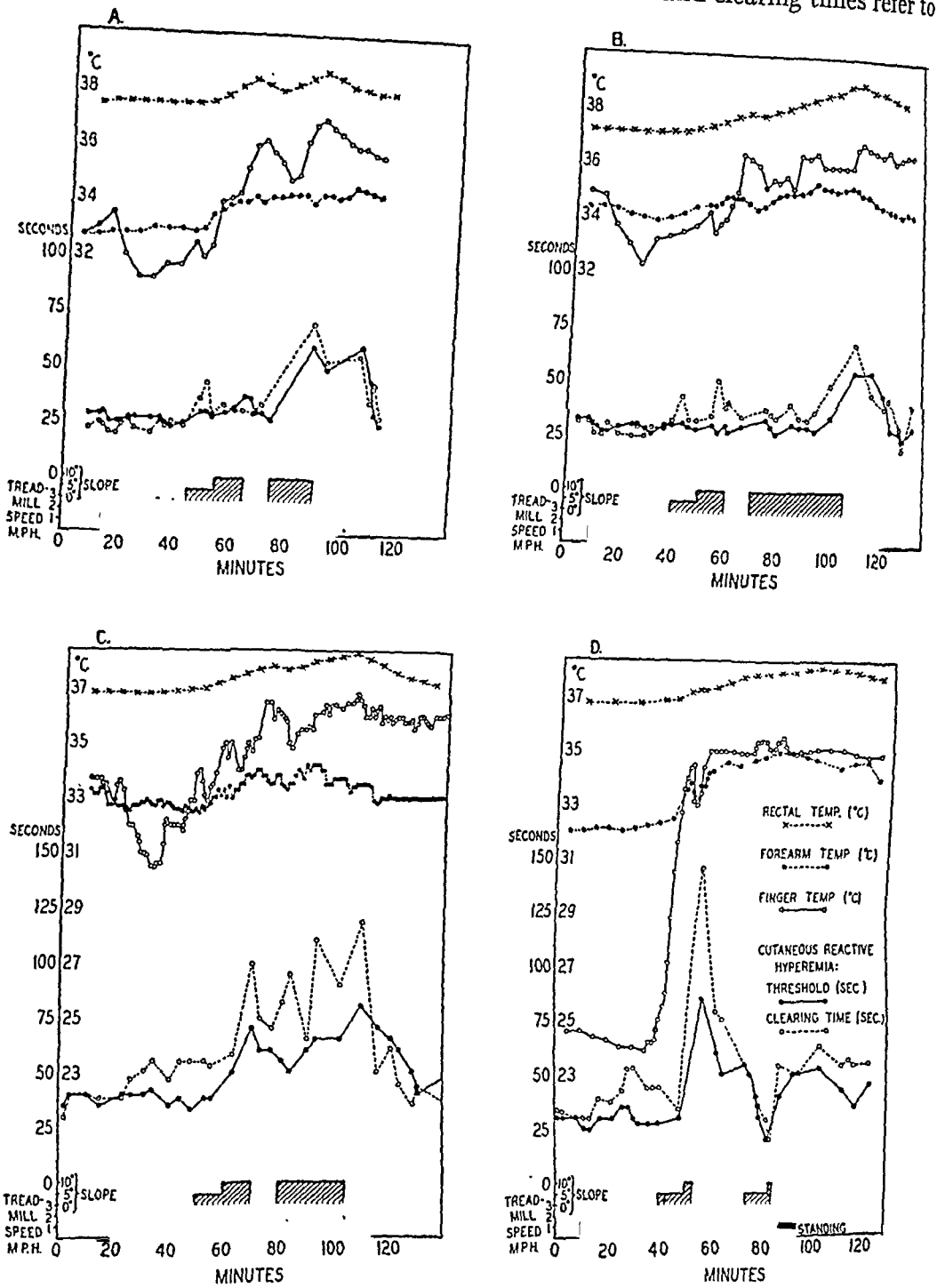

Fig. 2. CHARTS SHOWING EFFECTS OF EXHAUSTING WORK on threshold, clearing time, together with finger, forearm and rectal temperatures.

the end of these three periods and are expressed in terms of percentage increase above control values obtained previously in the same subject during rest. The total work, in terms of foot pounds, is indicated in the last column of table 2.

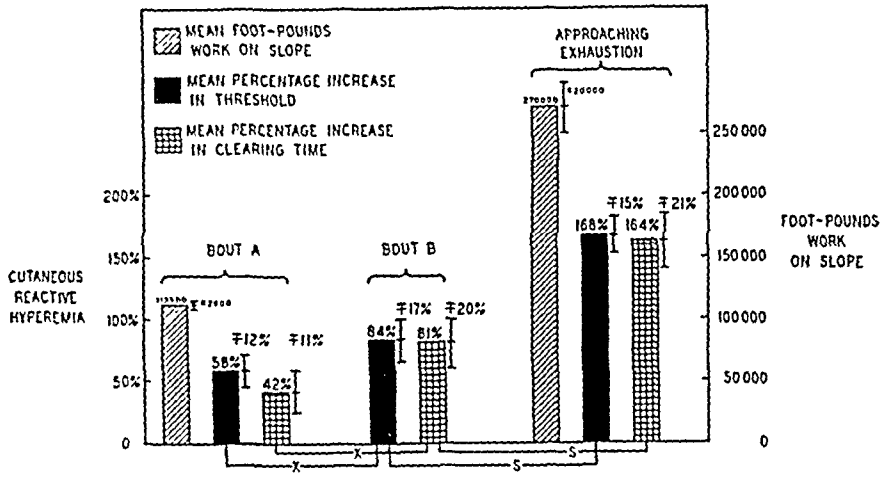

Fig. 3. CHANGES IN CUTANEOUS REACTIVE HYPEREMIA with exercise; summary of 17 experiments. ∓ = Standard error of the mean. X = Not a significant difference. S = A significant difference.

TABLE 2. CHANGES IN CUTANEOUS REACTIVE HYPEREMIA DURING GRADED EXERCISE

SUBJECT AND DATE	THRESHOLD			CLEARING TIME			TOTAL WORK DONE	
	Bout A	Bout B	Exhaustion Bout C	Bout A	Bout B	Exhaustion Bout C	Bout A and Bout B (each)	To Exhaustion Bouts A, B, C
	% increase	*% increase*	*% increase*	*% increase*	*% increase*	*% increase*	*Ft.-lbs.*	*Ft. lbs.*
J.S., 11/15/46	23	79	140	27	82	82	105,600	253,100
J.S., 11/20/46	115	90	200	110	75	175	105,600	281,600
J.S., 12/3/46	25	61	168	0	33	93	105,600	281,600
J.S., 12/9/46[1]	43	43	305	12	60	80	105,600	297,600
J.S., 1/15/47	0	7	97	43	21	115	105,600	357,600
E.L., 12/16/46[2]	200	97	200	380	83	380	71,800	71,800
L.S., 11/16/46	36	82	150	0		100	127,800	363,800
L.S., 11/18/46	0	0	182	0	0	275	127,800	482,800
L.S., 11/25/46[1]	185	252	252	100	300	300	127,800	255,300
L.S., 12/10/46[2, 3]	175	275	275	190	220	220	127,800	221,300
L.S., 1/16/47	21	67	67	20	80	80	127,800	255,600
W.G., 11/19/46	80	92	140	38	38	173	114,000	265,000
W.G., 1/22/47[2]	100	100	100	100	66	66	114,000	190,000
R.K., 1/23/47	48	140	140	50	200	200	103,500	207,000
M.E., 12/6/46	84	71	110	125	125	150	124,400	321,400
T.B., 11/25/46	110	140	200	25	75	200	110,200	220,400
F.S., 12/4/46	43	43	130	38	38	100	96,800	268,000
Average	58	84	168	42	81	164	113,500	270,200
S.D. (±σ)	46	62	63	40	79	87	10,870	75,500
S.E. of mean (∓)	12	17	15	11	20	21	2,900	20,200

[1] Two hours after 500 cc. venesection. [2] In these experiments the work done was less in *Bout B*, and hence, figures are excluded from the averages. [3] After a mild alcoholic celebration.

These data suggest that the conditions producing the increase in tone of the cutaneous vessels are cumulative in nature, but changes were not statistically significant until the approach of exhaustion. This is illustrated in figure 3, which presents the means from table 2 with their standard error. The mean elevation of threshold was 58 per cent for *Bout A* and 84 per cent for *Bout B*, with clearing times of 42 per cent and 81 per cent respectively. On the other hand, the third portion of figure 3 illustrates the marked and statistically significant increase in threshold and clearing times which occurred as the subjects continued to exercise until the approach of exhaustion. Here the average threshold was elevated by 168 per cent, and the average clearing time by 164 per cent, indicating a marked increase in tone requiring a much longer period of occlusion to produce visible reactive hyperemia.

Other Evidence of Cutaneous Vasoconstriction in Exercise. In general, skin temperatures were of limited value in estimating changes in the state of the cutaneous vessels because of *a*) thermal lag and *b*) differences in response of the vessels in the skin and underlying muscle. The effects of sweating were unimportant owing to the rubber dam over each thermal junction. With the onset of exercise the temperatures of the finger tips usually fell slightly (figs. 1, 2), and then gradually rose above control levels, while forehead and forearm temperatures rose as heat production increased. Only in one case (fig. 2*D*) was the cutaneous constriction sudden and severe enough to produce a pronounced drop in the temperatures of both the forearm and the finger.

As an independent check on the state of the cutaneous vessels, histamine was employed to evoke the 'triple response.' In agreement with Lewis (13) it was noted that the flare normally appeared in about 30 seconds, and the wheal in $1\frac{1}{2}$ to 2 minutes in the resting subject, and also early in exercise. However, at the time when threshold began to rise the flare appeared more slowly and less intensely. If histamine was punctured into the skin of the forearm at the time when threshold was maximally elevated, only a ghost or cyanotic flare was visible, which indicated a marked reduction in cutaneous blood flow. Moreover, as exhaustion approached, wheals appeared more slowly and tended to persist for a longer time.

Relation Between Rise of Venous Pressure in Exercise and Increase of a) Heart Rate and b) Respiratory Minute Volume. Heart rates and respiratory minute volumes were included to determine whether either of these might show sharp increases corresponding in timing and magnitude to the changes of tone in the cutaneous vessels. No correspondence of this type was found, but the relation of both heart rate, and respiratory minute volume to venous pressure was quite striking.

Bainbridge (14) found that raising the venous pressure, *measured in the femoral vein* of anesthetized dogs, led to an increase in heart rate. Although the

importance of the Bainbridge reflex has been questioned by some (15), the increase in heart rate with elevation of venous pressure has been confirmed by others (16, 17); and, Bock and Dill (18) state that it is "the principal cardiac reflex brought into play during exercise." We were unable to find any specific expression in the literature for the correlation between the rise of venous pressure and heart rate in exercise. Figure 1 suggests that this correlation may be quite close once venous pressure has begun to rise, e.g., at 3 miles per hour and 5° grade. Figure 4 provides a more complete summary of this relationship from 6 experiments in which the regression line relates the rise in heart rate to

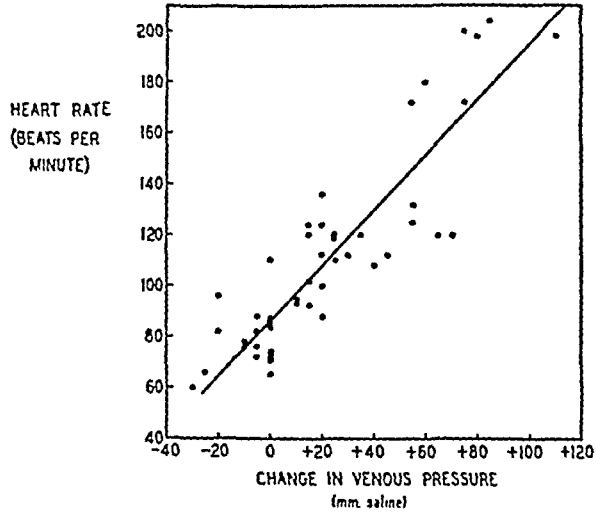

Fig. 4. RELATION BETWEEN PERIPHERAL VENOUS PRESSURE and heart rate during exercise on the treadmill. Venous pressures are expressed as differences between resting values for each subject and those at the end of each 10-minute period.

the increase in peripheral venous pressure. The correlation coefficient was 0.89, with p of less than 0.01.

Similarly, with respect to respiratory minute volume, Harrison (19) has found that he could increase the respiration of anesthetized dogs 50 to 100 per cent by rapid infusions of saline or blood, or by distension of a balloon in the right auricle. In 5 experiments on the treadmill, respiratory minute volume was measured for comparison with venous pressure. In figure 5 the changes in venous pressure and ventilation have been expressed in terms of fall or rise (mm. saline and liters per minute respectively) above or below the values observed in the same subjects during the control period. The correlation coefficient for respiratory minute volume vs. venous pressure is 0.89, with p less than 0.01.

Reactive Hyperemia During Tilting and During Venous Pooling. To estimate more clearly the degree of circulatory stress which would alter the response

of the cutaneous vessels to brief periods of occlusion, local cutaneous reactive hyperemia was studied during the less acute and less severe stresses of quiet standing on the tilt table, and also in recumbent subjects during passive congestion of three extremities. These experiments were performed in a constant temperature room (27° C.) on the same subjects, most of whom were also subjects for the treadmill exercise.

For the tilt-table experiments the subjects reclined on the horizontal table for 30 minutes or longer while threshold, clearing time, forearm and finger temperature, and heart rate were recorded. The subjects were then tilted to +70° for 30 minutes or longer. None of the subjects fainted during the procedure.

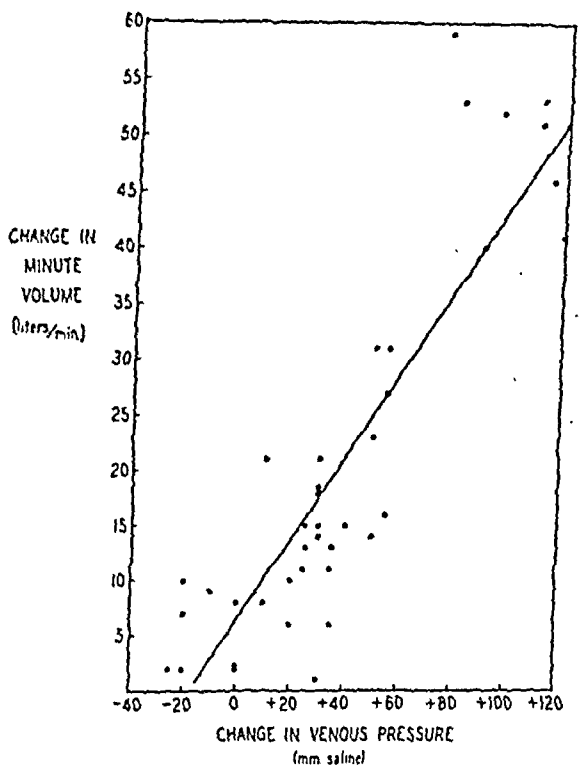

Fig. 5. RELATION BETWEEN PERIPHERAL VENOUS PRESSURE and respiratory minute volume during exercise on the treadmill. The figures are the differences between resting (control) values for each subject and those at the end of each 10-minute period.

The effect on cutaneous circulation in the forearm (table 3) was slight and inconstant compared to that seen in severe exercise. Only half the subjects showed changes in threshold or clearing time. The largest change recorded was 140 per cent increase in threshold on one subject, but this subject showed no measurable response on a second experiment. That the stress imposed was not great, is indicated also by the maximum heart rates, which exceeded 100 only in two instances.

Passive congestion of three extremities was produced by sudden inflation of cuffs to 75 mm. Hg after a 30-minute control period. Threshold, clearing time, forearm, and finger temperatures were measured throughout on the unoccluded extremity, and heart rate were recorded. Pooling of blood by this method for 30 minutes or longer produced even less change in cutaneous reactive hyperemia than did the stress of tilting; a rise in threshold and clearing time was consistently observed in only one subject (table 3). In none of the subjects was the maximum heart rate above 95.

Cutaneous Reactive Hyperemia in Resting Patients with Chronic Congestive Failure. Since there is still considerable difference of opinion concerning the state of the peripheral circulation in patients with congestive failure, localized reactive hyperemia was studied in the forearms of 12 *resting* patients with

chronic congestive failure, and compared with that of other patients of comparable age without any significant cardiovascular disease. The results are tabulated in table 4. With the exception of one patient (*no. 2*), there was no

TABLE 3. EFFECT OF TILTING AND VENOUS POOLING ON CUTANEOUS REACTIVE HYPEREMIA

SUBJECT	TILT-TABLE		PASSIVE CONGESTION	
	Threshold	Clearing time	Threshold	Clearing time
	% increase	*% increase*	*% increase*	*% increase*
J.S.	67	50	0	0
	33	23		
W.G.	43	0	0	22
	0	0	0	20
A.C.B.	0	0	200	17
			33	0
			100	21
L.H.S.	140	0	0	0
	0	0	0	0
E.M.L.	33	45		
M.E.	0	0		
F.W.S.	0	33	18	0
Average	32	15	35	8

TABLE 4. CUTANEOUS REACTIVE HYPEREMIA IN RESTING PATIENTS WITH CHRONIC CONGESTIVE FAILURE

(Controls performed at same time on patients of same age group but without significant cardiovascular disease)

CARDIAC PATIENTS					CONTROLS				
Patient	Age	Threshold	Clearing time	Temp. of test area	Control	Age	Threshold	Clearing time	Temp. of test area
		sec.	*sec.*	°C.			*sec.*	*sec.*	°C.
1	82	25	18	32.0	*1*	77	27	27	34.5
2	51	60	30	30.8	*2*	55	30	20	34.5
3	73	30	30	32.7	*3*	77	30	28	33.0
4	47	30	25	34.0	*4*	46	35	25	33.0
5	54	20	15	34.1	*5*	55	25	25	34.0
6	63	18	15	31.0	*6*	59	35	25	33.0
7	80	25	28	35.0	*7*	77	32	27	34.5
8	46	25	21	33.0	*8*	44	15	18	33.0
9	65	25	25	35.0	*9*	66	20	20	34.0
10	57	15	24	33.5	*10*	56	10	14	33.5
11	75	33	33	34.0	*11*	73	10	30	32.8
12	65	25	25	34.0	*12*	66	33	40	32.8
Mean	63.2	27.6 $\pm\sigma = 11.6$	24.1 $\pm\sigma = 5.9$	33.3 $\pm\sigma = 1.3$		62.6	25.2 $\pm\sigma = 9.3$	24.9 $\pm\sigma = 6.7$	33.6 $\pm\sigma = 0.7$

significant difference in threshold and clearing times between cardiac patients at rest and the controls, despite the fact that 6 of the patients were dyspneic at rest with high venous pressures, one was recovering from pulmonary edema,

and the others were dyspneic with slight exertion. The temperatures of the test sites on the forearms were very similar in the two groups.

DISCUSSION

In agreement with Schneider and Collins (4) an elevation of peripheral venous pressure was observed during exercise in healthy, young individuals, the rise of venous pressure being roughly proportional to work intensity. Conflicting results in earlier studies (1–3) can be ascribed either to the use of less accurate, indirect methods of measuring venous pressure or to differing grades of exercise. In addition, the treadmill has the advantage of offering untrained subjects the most familiar and physiological type of exertion, and consequently offers less interference with venous return by straining and by involuntary performance of a Valsalva manoeuver which less familiar exercise may produce.

Although these observations were not designed to study the mechanisms responsible for this rise in venous pressure, mechanical factors can be excluded. Tensing of the forearm muscles was avoided by resting the flexed forearm on a horizontal platform at the level of the xiphoid. Moreover, in agreement with Lyons *et al.* (20) purposeful contraction of the forearm muscles during measurements did not affect venous pressure significantly. Furthermore, the marked distention of the neck veins would indicate the more general nature of the rise in venous pressure. In any case, we may state that exercise elevates venous pressure in the upper extremities and adds the possibility that venous distention as well as cumulative filtration of fluid accompany exhausting exercise and may be concerned in the major compensatory adjustments of the circulation during exercise.

The duration of local vascular occlusion required to produce a clearly visible ring of reactive hyperemia in the skin of the elevated forearm (threshold, table 2) was increased by averages of 58, 84 and 168 per cent respectively at the end of moderate, severe and exhausting cumulative exercise on the treadmill. Reactive hyperemia, once visible, also persisted for longer times as exhaustion approached (clearing time, table 2). Earlier studies (12) indicated that both threshold and clearing time are prolonged when heightened vasconstrictor tone, increased by epinephrine or by cold, opposes the local dilator effect of metabolites. It may be concluded, therefore, that severe exercise can lead, in normal subjects, to constriction of the cutaneous as well as the renal (8, 9) vascular bed. This conclusion is supported by the delayed response to histamine.

The amount of exercise required to increase vasoconstrictor tone in the skin seems to be considerably greater than that required to reduce renal plasma flow. It has been reported (8) that walking on a treadmill for 10 minutes at 3 miles per hour at 5 per cent (approximately 3°) grade reduces renal plasma flow slightly but definitely. In contrast, the threshold of cutaneous reactive hy-

peremia was not modified significantly by the initial period of 10 minutes at 3 m.p.h. and 5° grade, sometimes increased by 10 minutes at 3 m.p.h. and 10° grade, but uniformly increased only when the latter severe exercise was continued to the point of fatigue or approaching exhaustion. This delay of cutaneous vasoconstriction, relative to the renal vasoconstriction, can be explained on the basis that heat production and rising body temperature throughout exercise would simultaneously tend to eliminate or reduce vasoconstrictor impulses to the cutaneous vessels.

The stimulus which produces this late increase of cutaneous vasoconstrictor tone must be relatively powerful, because it overcomes the usually predominant thermoregulatory mechanism. The stimulus is also apparently cumulative because a considerable period of severe exercise is required. Though central effects of the chemical products of muscular activity, e.g., lactic acid, cannot be excluded, the prior elevation of venous pressure for a considerable time suggests that lessening of blood volume by filtration may be partly responsible. Venous pressure was generally higher during the second bout of 3 m.p.h. at 10° and marked increase of threshold for reactive hyperemia also appeared during this period as exhaustion approached.

It has been estimated (5) that if venous pressure is raised throughout the whole body by 100 mm. above the previous resting level, fluid could be filtered from the blood stream at a rate of 25 to 30 cc. per minute or 250 cc. in a 10-minute period thereby decreasing available blood volume by this amount in addition to that made 'ineffective' by the greater volume of distended veins.

Increased filtration during exercise is probably chiefly responsible for the increased hematocrit and total plasma protein reported by most workers (21–24) and for the decreased blood volume demonstrated in more recent studies (21, 22). Two subjects (*J. S.* and *L. H. S.*) were exercised within 2 hours after each had donated 500 cc. of blood for transfusions. One subject (*J.S.*) noted no subjective differences from previous bouts and the responses of his cutaneous vessels were unchanged, despite the blood loss. The other subject (*L. H. S.*) noted earlier fatigue, while threshold and clearing times rose markedly during the first period of 3 m.p.h. at 10°, an unusual response for this subject. Similar results were obtained on the same subject after a moderate intake of alcohol the night before, which may have led to some dehydration. The evidence that reduction in blood volume is the stimulus is still not conclusive.

White and Rolf (9) have suggested that renal vasoconstriction in light to moderate exercise is due to vasoconstrictor nerve impulses, while the constricting action of epinephrine is added only when exercise becomes more severe. The latter may explain the belated, but marked, increase of cutaneous vasoconstrictor tone. In this respect it is interesting that iontophoresis of 1:50,000 epinephrine for 30 seconds elevated threshold by 171 per cent, i.e., by approxi-

mately the same amount observed in exhausting exercise. It is not possible as yet to identify the nature of the vasoconstrictor mechanism itself, viz., vasoconstrictor nerve impulses, epinephrine, pitressin or renin. Christensen *et al.* (10) described a brief, neurogenic vasoconstriction in the finger tips which lasted for a few minutes after the onset of moderate or severe exercise and then gave way to the usual thermoregulatory vasodilatation. This was observed also in the finger tips in these studies (figs. 1 and 2) because digital temperatures tended to fall until the subject began to walk at 3 miles per hour on the level and then rose more and more steeply as rectal temperature increased. During exercise the arteriovenous anastomoses of the fingertips and the cutaneous arterioles of the forearm may react differently to the opposing forces of vasoconstriction and thermoregulatory vasodilatation. As shown in figures 1 and 2, mild exercise was accompanied by a fall of digital temperature, while forearm temperature and reactive hyperemia remained constant. Conversely, as exhaustion approached, digital temperatures continued to rise with rectal temperature (one exception), while evidence of vasoconstriction developed in the skin of the forearm and the temperature of the forearm remained relatively constant despite rising rectal and digital temperatures.

It must be emphasized that in all the observations here described the forearm was elevated so that the tested area of skin was 30 cm. or more above the level of the interclavicular notch. In a few early observations, where reactive hyperemia was tested with the forearm at the side, with the tested skin near the level of the xiphoid, threshold and clearing time first decreased as peripheral venous pressure rose and then secondarily increased again to normal or well above normal as exhaustion appeared. It has been shown (12) that threshold decreases whenever local venous pressure rises and passively distends the subpapillary venous plexus to which skin color is largely due. In the present studies the forearm was elevated so that any change in venous pressure produced by exercise could not penetrate to the test area. This eliminated any temporary and mechanical lowering of threshold and the relation between reactive hyperemia and exercise then became more consistent as indicated in table 2.

Both threshold and clearing times are also increased greatly by any reduction of local skin temperature, but the changes in exercise cannot be ascribed to this factor because the temperature of the skin of the forearm was constant, or rose slightly as exercise progressed. Such slight reductions of temperature as occurred during vasoconstriction were much too small to explain the large rise in threshold. In fact, the lag in the skin temperature of the forearm was so great that, in this area, reactive hyperemia proved to be a much more sensitive indicator of temporary increase of vasoconstrictor tone and, hence, was more helpful in detecting changes which appeared suddenly and lasted for only brief periods.

The probable importance of change of venous pressure in the adjustments to moderate and severe exercise is indicated also by the relation between venous pressure, heart rate and pulmonary ventilation. To determine to what extent these relations depend on each other or upon another common factor in the background, will require further study.

The adjustments of cutaneous circulation to the stress of severe exercise are more marked than those produced by the lesser stresses of quiet standing on a tilt table and, during recumbency, by congestion of 3 extremities (table 3). These stresses affected cutaneous reactive hyperemia only in some subjects and then not uniformly.

In patients with chronic congestive heart failure, the state of the cutaneous circulation is still uncertain (25–27). Marsovsky (28) stated that the digital temperatures of normal subjects rose above control values during the reactive hyperemia which followed a 2-minute arterial occlusion but found no rise, or a delayed rise, in patients with cardiac failure. In a series of patients (table 4), 6 with dyspnea at rest, and 1 recovering from pulmonary edema, local reactive hyperemia produced by the occluding ring showed no change in the skin of the elevated forearm. All of these patients were studied while at rest in bed so that none had further elevations of venous pressure above their resting level, such as were produced by exhausting exercise in normal subjects.

SUMMARY

Peripheral venous pressure and cutaneous reactive hyperemia were studied in the relaxed forearms of healthy, male subjects exercising to exhaustion on the treadmill. The changes in cutaneous circulation during exercise were compared with those occurring during less acute or chronic types of cardiovascular stress: *a*) tilting to +70° for thirty minutes, *b*) venous congestion of three extremities, and *c*) chronic congestive failure in patients. During walking at rates of 1.5 to 3.0 m.p.h. on the level, venous pressure remained approximately constant. Venous pressure rose by an average of 30. mm. H_2O during walking at 3.0 m.p.h. and 5° grade, 73 mm. H_2O at 3.0 m.p.h. and 10° grade and 91 mm. H_2O during a second bout at the latter grade. The elevation of venous pressure was related to work intensity and also to the total amount of work done. The duration of local vascular occlusion required to produce a clearly visible ring of reactive hyperemia in the skin of the elevated forearm remained within normal limits until moderate exercise was performed. Threshold increased by averages of 58, 84, and 168 per cent respectively at the end of moderate, severe and exhausting exercise. This indicates that in severe exercise, as exhaustion approaches, the cutaneous vessels constrict markedly.

Tilting to +70° and, in recumbent subjects, venous congestion of three extremities produced much less striking changes in cutaneous reactive hyperemia. Threshold and clearing times were elevated only in some subjects

and to a much smaller degree than in exercise. Cutaneous reactive hyperemia was normal in 12 *resting* patients hospitalized for chronic congestive failure despite the fact that six of the patients were dyspneic at rest, one was recovering from pulmonary edema, and the others were dyspneic with slight exertion. A close correlation was noted between *a*) venous pressure and heart rate during exercise and *b*) venous pressure and respiratory minute volume during exercise.

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Reliability of Rectal Temperatures as an Index of Internal Body Temperature

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IN DETERMINING RECTAL TEMPERATURES in this Laboratory in the past it has been assumed that the distance from the anus at which rectal temperatures are recorded is not critical beyond a depth of 2 to 3 inches. A seemingly paradoxical observation has been made, however, which opens this assumption to question. Temperatures recorded at the tip of a flexible rectal catheter, passed 6 inches, on many occasions have been as much as 1° F. lower than temperatures recorded immediately thereafter at shallower insertions. In view of the important rôle that rectal temperature has in clinical and physiological studies as an index of deep body temperature, it was considered important to report this discrepancy and to undertake studies which might elucidate this phenomenon and indicate its influence on the rectal temperature as an index of internal body temperature.

Reference to this problem has not been found in reported work. Benedict and Slack (1) in their monograph on body temperature fluctuations described the gradient of rectal temperature to a depth of approximately 5 inches. They found that from the anus inward the temperature rose to the highest point at a depth of approximately $2\frac{1}{2}$ inches. They report no fall in temperature beyond this point. In many reports no mention is made of the depth at which rectal temperature is recorded; in some, 'deep rectal' temperatures are recorded but not further defined.

MATERIALS AND METHODS

A rectal catheter was constructed with five copper-constantan thermocouples, one at the tip, and others 2, 3, 4 and 5 inches from the tip. In use, the tip of the catheter was inserted 8 inches through the external anal sphincter so that temperatures were obtainable 3, 4, 5, 6 and 8 inches along the catheter from the anus. The thermocouples were made by twisting together carefully cleaned no. 20 stranded copper and no. 20 stranded constantan wire. These

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[2] In cooperation with the Medical Department, U. S. Army.

were soldered to brass couplings at the intervals described along the catheter. One constantan wire served as a common lead for all of the thermocouples. The brass couplings were coated with Glyptal lacquer so that the copper circuits were insulated from each other. The independent copper wires ran in a 10-foot cable to a rotary selector switch housed in a wooden box packed with Fiberglas to prevent air circulation. The reference junction thermocouple was formed by the common constantan wire twisted and soldered to no. 20 stranded copper wire. The copper lead from the switch and the copper lead from the reference junction thermocouple ran to a precision potentiometer. A similar independent circuit was made including a single thermocouple soldered to a small brass plug within the tip of a Levine stomach tube. The two reference junctions were immersed bare in separate thermos bottles 5 inches below the surface of crushed ice and water. The crushed ice extended to the bottom of the thermos bottles. The ice baths were agitated before each set of readings. The only soldered joints in the circuits were at the thermocouples and in the selector switch.

The thermocouples were calibrated against a precision thermometer in a well-agitated water bath controlled to $\pm 0.025°$ F. Each couple was placed directly beside the bulb of the thermometer for each reading. The calibration was carried out over the course of the experimental period and checked afterward. The range of temperatures included in the calibration was from 87° to 103° F. Each determination was triple-checked. The temperatures recorded in this report are considered accurate to $\pm 0.05°$ F.

The effect of conduction along the rectal catheter was studied by immersing the catheter in one water bath held at 99.5° F. $\pm$ 0.05° to a depth of 8 inches and the section of the catheter above the surface of the bath in another water bath. When water at 105° F. filled the upper bath, the temperature at the 3-inch point on the catheter rose 0.2° F. in 15 minutes. The temperatures further along the catheter remained unchanged. When the temperature of the upper bath was then changed to 65° F. the temperature at the 3-inch point dropped 0.5° F. in 10 minutes and continued at this level. The temperature at the 4-inch point dropped 0.1° F. in 7 minutes and remained at this level. The temperatures at the 5-, 6- and 8-inch points remained unchanged. Because of the effect observed at the 3-inch point, the temperatures recorded at this point are unreliable in *experiments 5* and *6* described below.

Pelvic x-ray photographs were taken to ascertain the position of the catheter in the pelvic cavity.

EXPERIMENTAL RESULTS

Position of Rectal Catheter in the Pelvic Cavity. With the first pelvic x-ray films taken with the rectal catheter inserted 8 inches, it became apparent that

the five points along the catheter could not be considered to be at graded depths within the rectum and sigmoid. Figure 1 shows the variation of position of the catheter in four individuals. In three of the individuals two separate insertions are shown. In all but one instance, the position of the catheter on postero-anterior and lateral films remained in the region of the rectum. In only one instance had it passed into the sigmoid. In the remaining instances, the general course of the catheter, in from the anus, is upward and anteriorly, slightly to the left or right of the midline for 3 to 4 inches. From this point on, it curves quite abruptly toward the opposite side and posteriorly, terminating an inch or so anterior to the lower third of the sacrum and 1 to 3 inches beyond the midline. An almost random distribution of the five thermocouples in the rectum is afforded but, in general, the more shallow thermocouples tend to be several inches anterior to the sacrum, while the ones near the tip are near the posterior

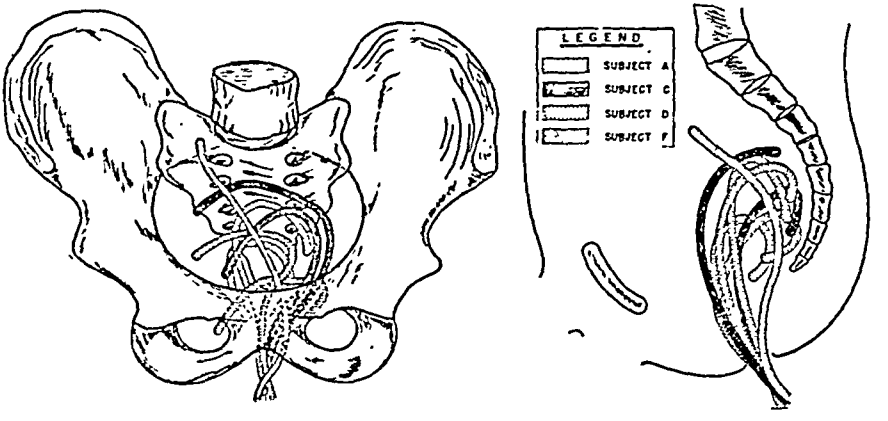

Fig. 1. POSITION OF EIGHT-INCH FLEXIBLE rectal catheter after 7 separate insertions in 4 individuals.

wall of the pelvis. The variability of position of the thermocouples on successive insertions in the same individual is reflected in variations in the sequence of temperatures observed along the catheter. In general the thermocouples 'farther in' give temperatures lower than the more 'shallow' ones, but the tip temperature is not consistently the lowest, nor the temperature at 4 inches consistently the highest. The maximum difference of temperature within the rectum was not necessarily recorded with every insertion. This was demonstrated clearly when reinsertion of the catheter, following a period in which the five temperatures remained relatively constant, resulted in a new distribution of temperatures with a decreased or increased maximum difference between the points.

Distribution of Five Rectal Temperatures in Men at Rest in Comfortable Ambient Conditions. Rectal temperatures were recorded in 5 young adult males,

seated and wearing ordinary clothing. The room temperature was 75° F. ± 5°. Five minutes after the catheter was inserted the five rectal temperatures were recorded. Three sets of readings were made at two-minute intervals. Results are presented in table 1. The greatest temperature difference observed at any one time under these conditions varied from 0.1° F. in *Subject B* to 0.6° F. in *Subject C*. The average of the temperature differences in the 5 individuals was 0.27° F.

Distribution of Rectal Temperatures in Men After a Two-Hour Exposure at 55° F. Sitting in Underwear-Shorts. The procedure of temperature measurement was the same as in *experiment 1*. Results are presented in table 1. The maximum temperature difference remained at 0.4° F. in *Subject A*, increased in *Subject B*, *D*, and *E*, and decreased from 0.6° to 0.5° F. in *Subject C*.

TABLE 1. COMPARISON OF DISTRIBUTIONS OF FIVE RECTAL TEMPERATURES IN MEN RESTING IN COMFORTABLE AMBIENT CONDITIONS AND AFTER A TWO-HOUR EXPOSURE AT 55°F. SITTING IN UNDERWEAR SHORTS

SUBJECT	COMFORTABLE AMBIENT CONDITIONS						AFTER 2 HR. AT 55°F. IN UNDERWEAR					
	Depth of rectal insertion, inches					Maximum temp. diff.	Depth of rectal insertion, inches					Maximum temp. diff.
	8	6	5	4	3		8	6	5	4	3	
A	97.9	98.3	98.2	98.1	97.9	0.4	97.3	97.4	97.7		97.7	0.4
B	98.9	98.9	98.9	99.0	98.9	0.1	99.1	98.9	99.3	99.4	99.6	0.7
C	98.1	98.5	98.5	98.7	98.7	0.6	98.6	98.5	98.9	98.5	98.9	0.4
D	98.9	98.9	99.0	99.0	99.1	0.2	98.3	98.6	98.9	98.8	98.7	0.6
E	99.1	99.1	99.2		99.1	0.1	98.4	98.1	98.4	98.3	98.5	0.4

The range of maximum temperature differences in the five subjects was from 0.4° to 0.8° F. The average of the temperature differences was 0.48° F.

Immediate Effect of Change of Posture on Distribution of Temperatures Within the Rectum. In the course of experiments in this Laboratory in the past, it has been noticed that rectal temperatures taken at the tip of a catheter inserted 4 to 6 inches may be altered abruptly when a subject changes from a sitting to a standing position. To study this effect, immediately following *Experiments 2* and *3*, the subjects stood for three sets of readings over a five-minute period, and then sat again for another series of readings. In only one instance out of ten was a difference of greater than 0.1° F. noted. In this instance the temperature at the 6-inch point dropped 0.5° F. between readings and remained at this level until the subject sat down, when the temperature rose abruptly 0.3° F. The temperatures at the other four points remained essentially unchanged during this period.

The effects of posture on body temperature over much longer periods of time have been reported and represent a different phenomenon from the abrupt

change observed here. The most reasonable explanation for this change is that the position of the catheter within the rectum changed from sitting to standing and that the thermocouple moved to a cooler region.

Distribution of Rectal Temperatures and Intragastric Temperature of Men Cooling at Rest Following Exercise (Fig. 2). The object of this experiment was to observe the distribution of rectal temperatures at reasonable extremes of body temperature and during the course of cooling, comparing these temperatures with intragastric temperatures. *Subjects F, G,* and *H* exercised until their rectal temperatures were approximately 102° F., sat nude first in an ambient temperature at 80° F. ± 5° and then at an ambient temperature of 40° F. ± 5° until the rectal temperature had dropped approximately 5° F. Temperatures were recorded at frequent intervals at five points within the rectum and at the tip of an intragastric catheter.

Subject F, 8 minutes after insertion of the rectal catheter and 10 minutes after exercise, had a temperature at the 8-inch point 0.7° F. higher than the next highest temperature. During the course of cooling the tip temperature became the lowest of the rectal temperature (discounting the temperature at the 3-inch point after entering the cold room because of conduction along the catheter). The maximum difference in rectal temperatures initially was 0.8° F. with the temperature at the 8-inch point the warmest, 0.6° F. higher than the next highest temperature. During the first hour of cooling, the maximum difference in rectal temperatures reduced to 0.1° F. After the subject entered the cold room, the maximum temperature difference gradually increased and at the end of the cooling period was 0.3° F. with the tip temperature now the lowest. The gastric temperature was the highest temperature throughout all but the initial 15 minutes of the cooling period. At no point was it more than 0.4° F. higher than the warmest rectal temperature. During two periods of moderate exercise of the lower extremities, all of the temperatures dropped abruptly, the gastric temperature falling with the rest.

Subject G initially had a maximum temperature difference of 0.2° F. along the rectal catheter. This difference remained between 0.2° and 0.3° F. for two hours of cooling. When the subject entered the cold room (40° F.), the maximum of difference in temperature (discounting the temperature at the 3-inch point increased to a final value of 0.9° F. The gastric tube was passed at the end of the first hour of cooling. The gastric temperature rose for 10 minutes and then cooled 1.8° F. during the next two hours, while the warmest rectal temperature cooled 2.5° F. and the coolest rectal temperature cooled 2.8° F. During this period the subject complained of hunger.

Subject H had an initial maximum temperature difference of 0.3° F. with the rectal tip temperature the coolest. During the first 25 minutes of cooling, the tip temperature fell 1.3° F. while the warmest rectal temperature fell

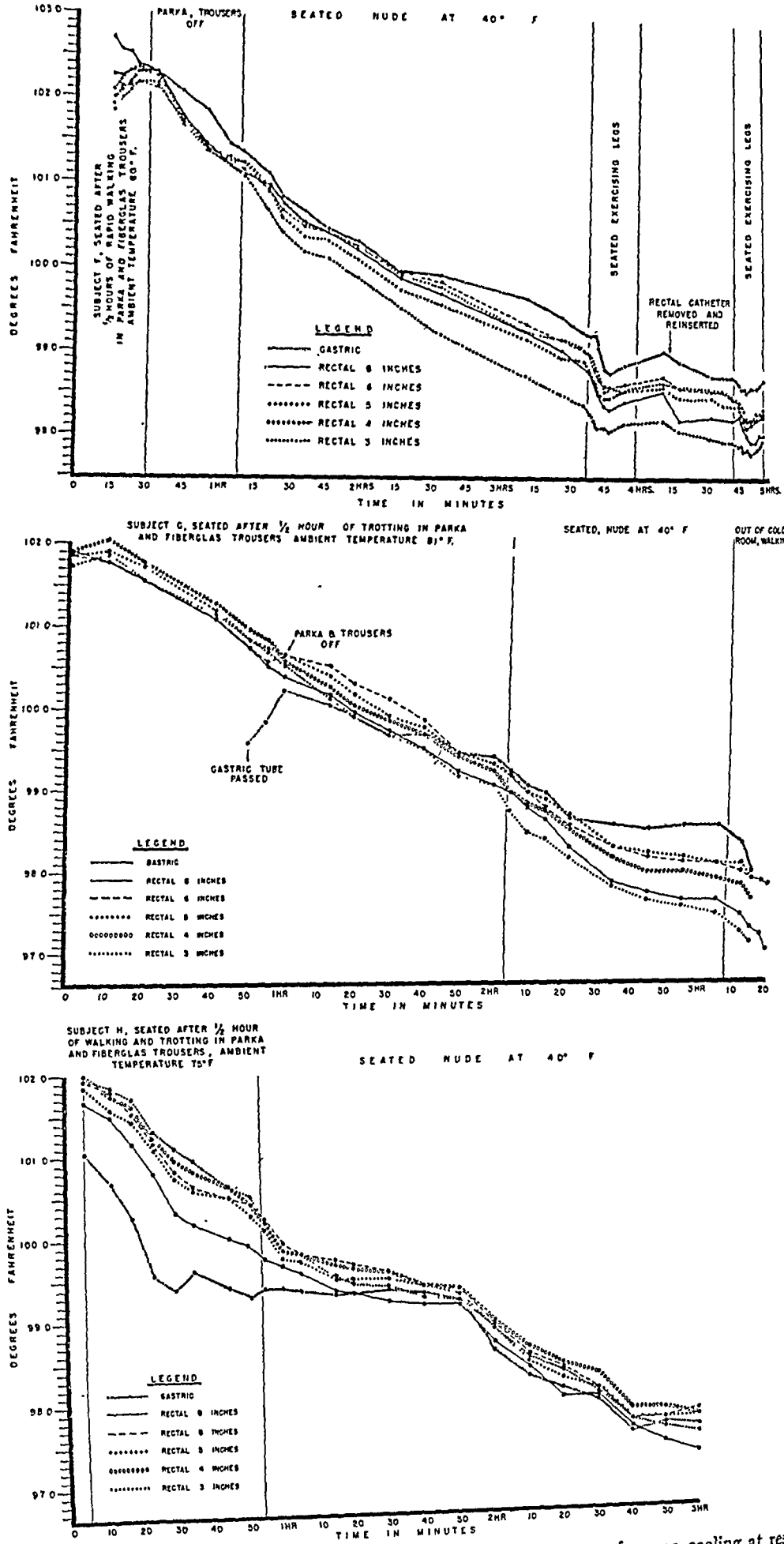

Fig. 2. DISTRIBUTION OF RECTAL AND INTRA-GASTRIC temperatures of 3 men cooling at rest following exercise.

0.8° F. The maximum temperature difference increased from 0.3° to 0.8° F. during this time. When the subject entered the cold room, the maximum temperature difference again decreased to 0.3° F., and finally increased again during the last 45 minutes to 0.6° F. The gastric temperature was initially approximately a degree cooler than the warmest rectal temperature. This difference decreased during the second hour, and for the last hour and a half it paralleled the warmest rectal temperatures remaining 0.2° to 0.4° F. lower than the warmest rectal temperature.

Effect of Immersion to Level of Umbilicus in Water at Varied Temperatures on Distribution of Rectal Temperatures and on Gastric Temperature (Figs. 3 and 4). Subject H, with rectal and gastric catheters in place, sat in water at 105° F. to the level of the umbilicus. The maximum temperature difference along the catheter remained 0.1° F. or less while, during the course of one hour, his warmest rectal temperature rose from 98.3° to 100.7° F. Cold water was then added to the bath, bringing the bath temperature to 80° F. ± 5° which felt 'comfortably cool' to the subject. All the temperatures fell approximately 2.5° F. over varying periods of time, and then leveled off or rose slightly. The fall of the gastric temperature was the most rapid: 2.5° F. in 10 minutes. The temperature at the 8-inch point on the rectal catheter was the next most rapid: 2.8° F. in 15 minutes. And the other rectal temperatures, which remained within 0.2° F. of each other, fell the slowest: 2.6° F. in 30 minutes. Both the gastric and the rectal 8-inch point temperatures rose from their minimum values 0.9° and 0.3° F. respectively for a period of 15 minutes, while the remaining rectal temperatures continued to drop (1.0° F.). During the period of rapid cooling the maximum temperature difference along the rectal catheter increased from 0.1° to 1.5° F. and then decreased again to 0.4° F.

Subject H remained in water approximately 65° F. for two hours. At the end of this period hot water was again added, bringing the bath temperature back to 105° F. For 20 minutes all of the rectal temperatures continued to drop, as did the gastric temperature, and the maximum difference between the rectal temperatures increased from 0.4° to 0.7° F. During this time the subject felt comfortable and did not sweat. Ten minutes later, when his maximum rectal temperature had risen from 96.5° to 96.7° F., perspiration was first noticed on the subject's forehead. As the rectal temperature rose, the maximum temperature difference decreased to 0.1° F. After this the temperature at the tip, which had been the coolest, became now the warmest of the five: 0.2° F. higher than the nearest temperature.

Effect of Temporary Interruption of Leg Blood Flow on Distribution of Rectal Temperatures. Subject H sat nude at 55° F. for three hours. During this period his warmest rectal temperature fell 1.5° F. from 99.8° to 98.3° F. Blood pressure cuffs around his upper thighs were then inflated quickly to 280 mm.

Hg and maintained at that level for 15 minutes. During the period of occlusion, the warmest rectal temperature, which was 3 inches from the anus, fell 0.2° F., while the temperature at the tip of the catheter at the 8-inch point, which

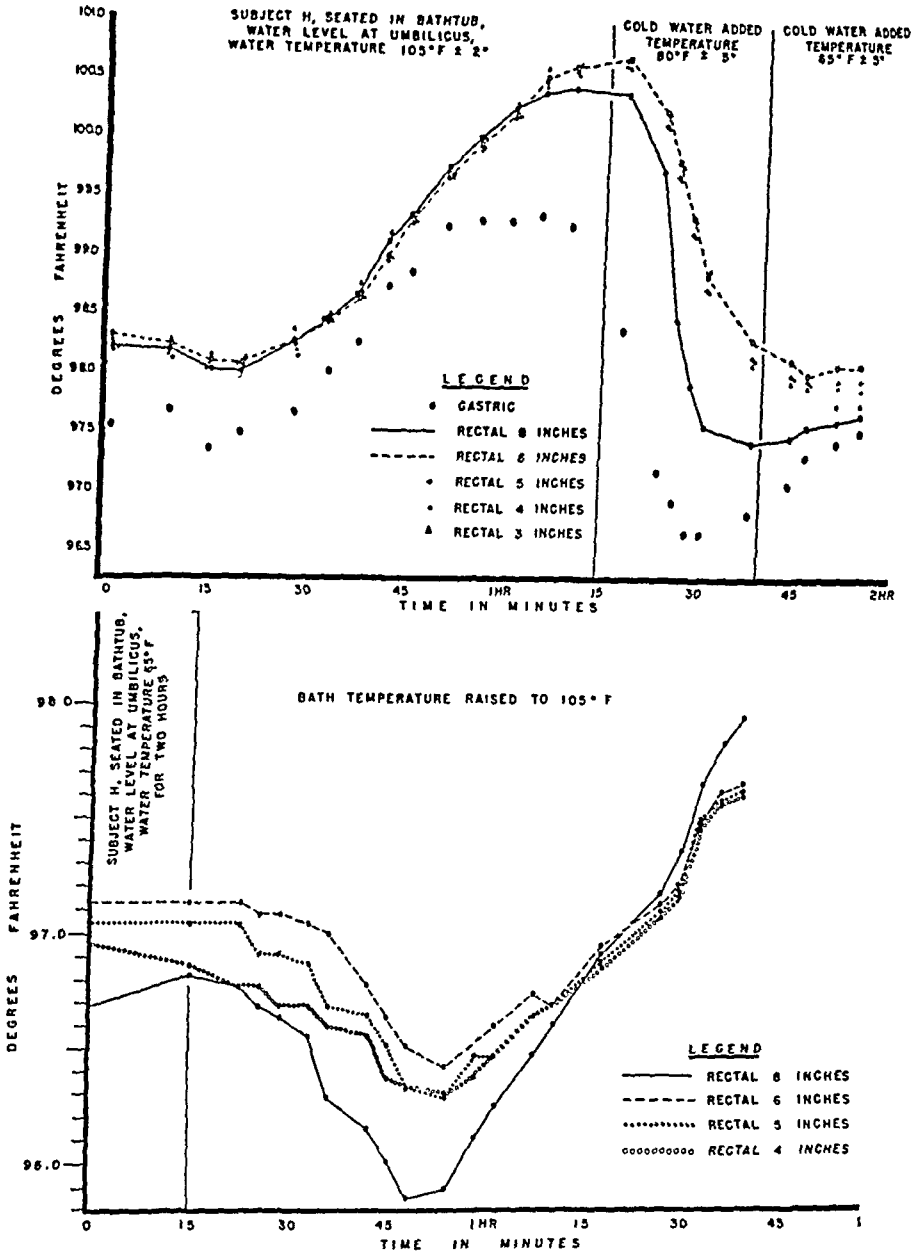

Fig. 3 (*upper*). DISTRIBUTION OF 5 RECTAL TEMPERATURES and gastric temperature in a man immersed to the level of the umbilicus in water at first warmer than any body temperature.

Fig. 4 (*lower*). DISTRIBUTION OF 4 RECTAL TEMPERATURES in a man immersed to the level of the umbilicus in water held at 65°F., plus or minus 5 for two hours and then raised to 105°F.

initially was 0.4° F. cooler than the temperature at the 3-inch point, dropped 0.1° F. and then rose again 0.1° F. The cuffs were then deflated. During the next 10 minutes the temperature at the 3-inch point dropped 0.1° F. while the temperature at the 8-inch point fell 0.5° F.

DISCUSSION

In 8 individuals, studied under a variety of conditions, temperatures near the tip of a flexible catheter inserted 8 inches through the external anal sphincter were in almost every instance lower than temperatures recorded at intermediate points along the catheter. The maximum difference in temperature along the catheter varied from 0.1° to 1.5° F. The greatest differences were observed in cases where body temperature was falling rapidly (e.g. 2.5° F. in 20 minutes), but differences of 0.6° F. have been recorded in individuals maintaining a relatively steady body temperature.

The position of the terminal portion of the rectal catheter, as determined by x-ray, suggested a possible explanation of this phenomenon which could be tested experimentally. In 6 out of 7 insertions of the catheter in 4 individuals, the tip of the catheter lay near the posterolateral wall of the pelvis. Adjacent to this region on the pelvic wall lies the network of the hypogastric vein and its branches which include blood flowing from the skin of the buttocks, the upper leg, and external genitalia. *Experiment 6* was planned to see if direct warming and cooling of these surfaces influenced the temperature toward the tip of the catheter to a different degree than the other rectal temperatures. The results show this to be the case. As long as the surface of the body below the umbilicus was subjected to a temperature higher than any body temperature, the tip rectal temperature did not drop below the other rectal temperatures. When this surface was subjected to temperatures lower than any body temperature, the temperature at the tip fell away from the remaining rectal temperatures and at one point was 1.5° F. below the other rectal temperatures.

The continued fall of all of the temperatures for a period of 20 minutes after the water temperature was again raised above internal temperature is a striking instance of what other workers have reported (2, 3), namely, that when individuals whose body temperatures were falling, passed from cold into warm environments, their internal temperatures continued to fall for a period of time. A likely explanation of this temperature drop is that a rise in skin temperature results in increased circulation through the cooled peripheral tissues of the body, cooling the blood and hence dropping the internal temperature. In *experiment 6* during this phase of further cooling which occurred after the water temperature had been raised above any internal temperature, the tip rectal temperature dropped more abruptly than the remaining rectal temperatures as might be expected. When, however, the internal temperature finally rose, the tip rectal temperature rose more rapidly than the other rectal temperatures and ultimately became the warmest of the five.

The results of *experiment 7* strengthen the conclusion that temperature of the blood in the vessels lying on the posterior pelvic wall account for the lower temperatures observed at the tip of the rectal catheter. Following interruption

of the blood flow to the legs by means of blood pressure cuffs high on the thighs, intense hyperemia of the cool skin of the legs was observed. During this phase the tip rectal temperature dropped 0.5° F., while the warmest rectal temperature dropped only 0.1° F.

Although the temperature of venous blood passing through the pelvis from the surface of the body probably played the major rôle in causing the deviations in rectal temperatures observed, it should be mentioned that the temperature of blood flowing in the arteries lying on the pelvic wall could be expected in most instances to have a similar effect. During body cooling, the temperature of arterial blood leaving the left ventricle can be expected to change more rapidly than most internal tissue temperatures. Nedzel (4) has shown this to be the case in dogs. He found that the temperature of the gastric mucosa, intestinal mucosa, and rectal mucosa all lagged behind changes in arterial temperature (approximately 15 minutes). Furthermore, Bazett *et al.* (5) have shown in men that during body cooling arterial blood is further cooled peripherally where arteries lie adjacent to veins carrying cooled blood from the body surface. These phenomena offer possible explanations of the precipitous drop in gastric temperature in *experiment 6*. Hyperemia of the gastric mucosa may have permitted a comparatively direct reflection of the temperature of circulating blood. Another explanation is that the gastric thermocouple was in proximity to the inferior vena cava, which carried cool blood from the surface of the body.

It was also the purpose of this work to determine whether or not the same influences which caused a lower temperature toward the tip of the rectal catheter also influenced the other rectal temperatures in the same direction, and hence caused deviations rendering the rectal temperatures at any depth unreliable as an index of the internal temperature. Two considerations suggest that this is not the case. Firstly, the influence causing the deviation is considerably localized, since at times the warmest rectal temperature was recorded at a point only 2 inches from the coolest temperature. This was true in *experiment 6*, when at one time the difference in temperature between these two points was 1.5° F. Secondly, the only veins in the pelvic cavity carrying blood directly from the surface of the body lie near the pelvic wall. Temperatures obtained anteriorly in the rectum near the midline should be sufficiently distant from the pelvic wall so as to be beyond the direct influence of cooled venous blood returning from the surface of the body. It should be pointed out, however, as H. C. Bazett *et al.* have done (5), that the effect of cool venous blood in the pelvic cavity on the temperature of the blood in arteries supplying the rectal wall might produce cooling in the rectum disproportionate to general body cooling. It has not been possible to assess this phenomenon in these experiments because of the unreliability of our other deep body temperature, i.e. intragastric (see below).

A consideration of the reliability of the rectal temperature as an index of internal body temperature brings into question the meaningfulness of the concept of 'an index of internal body temperature.' Bazett (6) has stated, "the conception that a man has an internal mass of tissue maintained at 37° C., surrounded by a thin layer with a steep temperature gradient, such that the surface temperature is about 33° C., is common but inaccurate." Apart from the difficult question of defining the mass of the body which lies beyond the direct influence of temperature gradients to the surface of the body, a consideration of the pattern of temperatures within this mass is complex. The temperature of any region in the internal mass of the body depends on the metabolic activity of the region, the temperature and amount of blood flowing through the region, and the gradients of temperature to surrounding regions. These factors vary between regions and within the same region. Variations in internal temperatures occurring at different points along the human intestinal tract have been reported. Hepburn *et al.* (7) found the average temperature in the sigmoid, taken through a sigmoidoscope, to be almost 2° F. higher than the temperature in the stomach and upper intestine. Foged (8) reported the average stomach temperature to be 0.4° F. lower than the rectal temperature. In dogs, Nedzel (9) found the average temperature of the surface of the liver to be 0.4° to 1.0° F. higher than the temperature of arterial blood. It is apparent that no single regional temperature could indicate, except by chance, the average of all of the internal temperatures. Furthermore, the deviation of a single regional temperature from other body temperatures or the average body temperature could be expected to vary with differing levels of activity and ambient conditions. Figure 3 illustrates the inadequacy of a temperature change in a single region of the body as an index of temperature changes in other parts of the internal body mass. For a period of 15 minutes two deep body temperatures, namely, an intragastric and a temperature at the tip of an 8-inch rectal catheter, rose 0.9° and 0.3° F. respectively, while during the same time, four other rectal temperatures had fallen 1.0° F. Eisenberg and Bazett (10) have also observed internal body temperatures changing in opposite directions simultaneously.

Of greater practical importance than the deviations of different regional temperatures from each other and from the average body temperature, is the problem of accurately positioning any temperature recording device, so as to obtain reliably the temperature of a single region. For if this is not accomplished, temperature differences recorded may represent temperature gradients in the body rather than temperature changes of a region. In superficial areas, such as the oral cavity or the axillae, positioning can be accomplished under direct vision. In more remote regions such as the rectum or the stomach, this is not possible. Our studies have convinced us of the shortcomings of a gastric temperature in this regard. We cannot say whether our gastric thermocouple

lies surrounded by liquid gastric contents, against the mucosa, or in the gas bubble. Masek (11) observing the position of a gastric thermocouple through a gastroscope noted a significant drop in temperature when the thermocouple was raised from the surface of the gastric contents into the gas bubble. Other local factors in the stomach render it unsuitable for deep temperature measurements. Masek showed that the stomach temperature rose following an injection of histamine which caused mucosal hyperemia, increased secretion and motility in the stomach. Following the injection of nicotinic acid, which caused gastric hyperemia without increased secretion or motility, the gastric temperature dropped. It is of interest in our experiments that *Subject G* complained of hunger during the last hour of cooling. During this period his gastric temperature rose relative to the rectal temperature.

The rectum also offers difficulties in positioning of a thermocouple. When a flexible catheter is introduced through the anus its position in relation to the posterior and lateral wall of the pelvis, where it is most likely to be influenced by cool blood, is unpredictable. Pelvic x-rays of 4 individuals, who had a flexible rectal catheter passed only 4 inches through the external anal sphincter, showed that the tip tended again to curve back near to the posterior wall of the pelvis.

By utilizing a rigid rectal catheter inserted at a fixed angle and in the midline, it should be possible to position a thermocouple sufficiently anterior in the pelvic cavity so as to be beyond the direct influence of the temperature of blood flowing in the vessels on the pelvic wall. The problem of maintaining a fixed position of such a catheter is considerable in men who must vary their posture from sitting at rest to walking. A special catheter has been constructed which makes this possible. A three-inch rigid plastic catheter is attached firmly to a plastic rod which is curved to fit the shape of the lower back between the buttocks. The upper end of this rod is attached to a flat plate, held against the small of the back in a canvas harness. The harness is adjustable so that a single catheter fits a considerable range of body sizes. A variety of postures including lying, sitting, standing and walking, may be assumed without appreciable discomfort or shifting of the position of the catheter.

SUMMARY

Studies were made to determine whether or not the distance from the anus at which rectal temperatures are recorded is critical beyond a depth of 2 to 3 inches. In 8 men studied under a variety of conditions of heat balance and imbalance, temperatures near the tip of a flexible catheter inserted 8 inches through the external anal sphincter were in almost every instance lower than temperatures recorded simultaneously at intermediate points along the catheter. Deviations observed varied from 0.1° to 1.5° F. and were greatest in individuals whose body temperatures were falling. X-ray films showed the tip of

the catheter in a majority of instances to lie near the posterolateral wall of the pelvis.

The experimental data suggested that cooled blood from the surface of the body passing through veins in the pelvic wall adjacent to the terminal portion of the catheter was responsible for the deviations observed.

The meaningfulness of 'an index of deep body temperature' was discussed, and the importance of accurate positioning of devices for recording internal temperatures was stressed. A rigid plastic catheter was described which permits reproducible positioning of a thermocouple against the rectal mucosa, sufficiently anterior in the pelvic cavity to be beyond the direct influence of the temperature of blood in the large vessels of the posterior pelvic wall.

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Mixing of Alveolar Air with Dead Space Air During Expiration

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HALDANE POINTED OUT that in order to obtain satisfactory alveolar air by his method the subject must expel some 800 ml. before the sample is taken (1), and he believed that if the sample were obtained after a smaller expiration there would be a danger of diluting the alveolar air with air from the dead space. He also stated that, at rest, a rise of .05 per cent CO_2 in the alveolar air occurs for each half-second delay in delivery (2). In assessing his conclusions one must remember that his subject delivered the samples immediately after inspiring and, moreover, that the issuing gas was sampled distal to the mouth. We have investigated the dilution of alveolar air obtained from the mouth, and in the course of doing so it has become apparent that it is a simple matter to obtain a sample which has the same tension of CO_2 as one obtained by the end-expiratory Haldane-Priestley technique.

The air which passes through the upper respiratory tract during expiration may be altered by factors other than mixing with dead-space air; for instance Galdston and Horwitz (3) showed that there was a slight modification of the composition of the gas in the supra-glottic space by equilibration with the glandular secretions.

APPARATUS AND PROCEDURE

The apparatus devised for these investigations is illustrated in the accompanying figure. The principle of the method is that about 100 ml. of gas are removed from the oral cavity at the end of a normal exhalation, and immediately after this a sample is withdrawn for analysis.

After the subject has the mouthpiece in position, and nose clip applied, the operator carries out the sampling by simply rotating a tap through 360° at the end of a normal expiration. During the rotation three different channels leading from the oral cavity are successively utilized. In the initial position the main channel leads from the mouthpiece to the external air via an L-shaped path through the tap, permitting normal respiration. The remaining channels lead from the mouthpiece, one inside the other. The outer provides a passage from the mouth through the central rotor portion of the tap to an evacuated

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rubber bulb, such as the Politzer Air Syringe no. 288, of 180-ml. capacity; it lies below the L-shaped passage and is the means by which some 100 ml. of air are evacuated from the oral cavity. It is so placed as to be opened up immediately after the communication to the outside air has been closed.

The inner piece of tubing leads from the mouth to the vacuum sampling tube. The latter is of special design (4) constructed so that one turn of its tap will first clear out 5 ml. of dead-space air from the sampling tube into one barrel and then take a 10-ml. sample into a second barrel, this being adequate for analysis by the Scholander method. A larger tube may be used if the Haldane gas analyzer is employed.

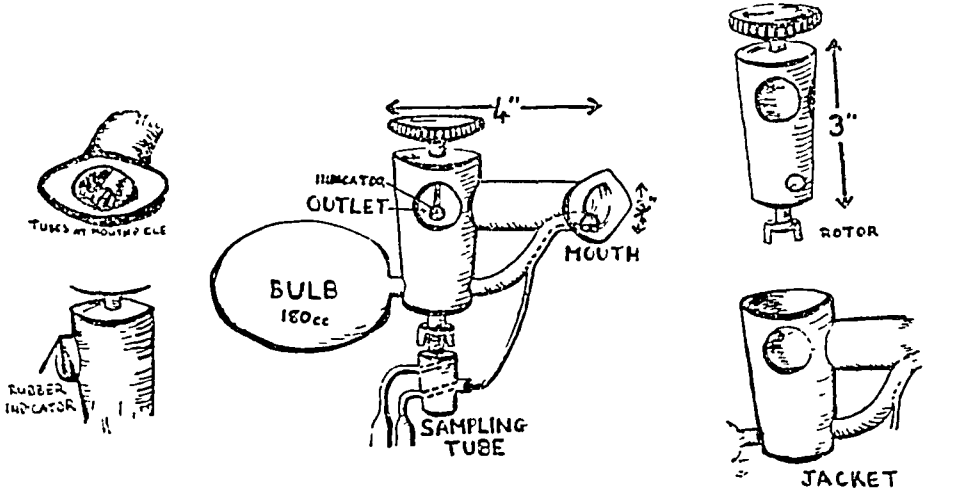

Fig. 1.

The glass tap of the sampling tube is clasped by a fitting which is attached to the lower end of the rotating part of the metal tap and is so placed that immediately after the evacuating bulb has withdrawn air from the upper respiratory passages the sampling tube is brought into communication with the oral cavity. When this occurs the dead-space of the tubing is first washed out, and then as rotation of the tap continues a sample is withdrawn for analysis. Finally, the full 360° of rotation are completed, and the subject is thus brought once more into communication with the outside air. The process of evacuation and sampling can be carried out in the space of a second, so that there is little, if any, interruption of normal breathing.

A small strip of latex sheeting is suspended at the outlet from the tap to indicate the phase of respiration, and the sample is taken just as the indicator drops back to center, that is, at the end of expiration. The rotation of the tap has been carried out manually, and this has been found quite satisfactory, but for special purposes, such as automatic sampling using a modified sampling tube,

it would be an advantage to incorporate a solenoid with clockwork or electric motor to carry out the rotation at the moment and at the speed required. The total dead-space of the apparatus is less than 25 ml.

RESULTS

Samples of alveolar air with a carbon dioxide content close to that found in Haldane-Priestley samples have been collected by the above method from a number of subjects. The results presented here were all obtained on one subject (*CW*) whose respiratory rate was usually about 10 per minute. He sat at rest in

TABLE 1. PERCENTAGE OF CO_2 IN SAMPLES OBTAINED FROM THE MOUTH WITH THE APPARATUS DESCRIBED: (A), WITH SUCTION; (B), WITHOUT SUCTION

Mean values of daily runs of 4 samples of each type

DATE	A. ORAL SUCTION	B. END-EXPIRATORY (WITHOUT SUCTION)	DIFFERENCE (A) - (B)
11.3.49	5.77	5.50	0.27
12.3.49	5.56	5.50	0.06
14.3.49	5.79	5.48	0.31
16.3.49	5.33	5.25	0.08
17.3.49	5.70	5.61	0.09
18.3.49	5.74	5.62	0.12
19.3.49	5.79	5.73	0.06
23.3.49	5.95	5.80	0.15
24.3.49	5.60	5.43	0.17
25.3.49	5.60	5.54	0.06
26.3.49	5.73	5.58	0.15
1.4.49	5.78	5.63	0.15
1.4.49	5.85	5.70	0.15
4.4.49	5.98	5.79	0.19
4.4.40	5.94	5.62	0.32
5.4.49	5.98	5.79	0.19
24.4.49	5.94	5.90	0.04
25.4.49	5.79	5.76	0.03
Mean			0.144
Standard error of mean			0.021

a chair and experiments were all carried out in the mornings, the subject having eaten no breakfast.

The term 'Oral Suction' is used for the procedure described above, 'End Expiratory' for the same procedure with the exception that the preliminary evacuation was not employed. The results of experiments in which 120 collections of alveolar air by two methods were made on one subject over a period of several months are shown in table 1. The Scholander method of analysis was used.

The results of a typical experiment in which 23 estimations of the carbon dioxide content were made on one subject during a morning are shown in table 2.

These results have not been specially selected; indeed we find that the variability of the results with the oral suction is considerably lower than with the Haldane-Priestley method, as is shown in table 3, which represents a series made over a period of several months.

Two short comparisons were made of end-expiratory Haldane-Priestley samples taken: *a)* while using a nose clip, and *b)* without a clip. In the first series there were four of each, with a mean difference of .1 per cent CO_2 between them; in the second there were four of each with a mean difference of .05 per cent CO_2, all those taken with a nose clip in each case being higher. Most of our instrumental comparisons were made with Haldane-Priestley samples taken

TABLE 2. PERCENTAGE OF CO_2 IN SAMPLES OF ALVEOLAR AIR

ORAL SUCTION	HALDANE-PRIESTLEY METHOD	ORAL SUCTION	HALDANE-PRIESTLEY METHOD
5.48	5.49	5.55	5.37
5.48	5.50	5.36	5.53
5.42		5.70	5.51
5.25	5.41	5.44	5.47
5.87	5.50	5.58	5.56
5.61	5.74	Mean 5.51	Mean 5.51
5.43	5.58	Standard error 0.047	Standard error 0.029

The first six samples were taken by oral suction at intervals of one minute. Then five Haldane-Priestley samples were taken at intervals of five minutes. The remaining twelve samples were taken by oral suction and Haldane-Priestley methods alternately at five-minute intervals.

TABLE 3. RELATIVE VARIANCE OF SAMPLES OBTAINED BY ORAL SUCTION AND HALDANE-PRIESTLEY METHODS

METHOD	NO. OF CASES	STANDARD DEVIATION OF PERCENTAGE OF CO_2
Oral suction	134	0.083
Haldane-Priestley	131	0.095

in the traditional manner with the nose unclipped, but in view of the results quoted which suggested contamination from the nasal passages, we used a clip for the later ones.

DISCUSSION

Many workers have felt that it would be an advantage to obtain samples of alveolar air without disturbing the subject's normal breathing, and automatic sampling devices have been constructed with this objective in mind. The samples obtained by these methods have apparently been diluted with varying amounts of air from instrumental and respiratory dead space, and the CO_2 tension has thus been lower than that obtained by Haldane's end-expiratory method which, in the opinion of many workers, gives a CO_2 tension very

close to that of arterial blood. Rahn (5), who has reviewed the automatic methods up to 1946 and whose own method is one of the most recent, found that his figures for CO_2 tension were, on the average, 2.5 mm. Hg lower than those given by the Haldane technique, and a similar difference was obtained by Barker *et al.* (6), who in addition found good agreement between the tension of CO_2 in arterial blood and that measured in alveolar air by the Haldane-Priestley method.

Lesser (7) has attempted to remove end-expiratory samples from the mouth by means of a tube leading to a sampling bottle, and has obtained samples on an average 1.6 to 4.1 mm. Hg below Haldane-Priestley samples.

Lambie and Morrissey's method (8) involved a preliminary suction procedure; close agreement between analyses of simultaneous samples was accepted as evidence that alveolar air was obtained.

We have recorded in one subject statistically significant differences between samples collected at the end of an expiration and those collected after preliminary evacuation of the oral cavity. This suggests that the lower CO_2 content of the end-expiratory samples was due to dilution with dead-space air from the upper respiratory tract, since there was no other known source of contamination: the instrumental dead space was small and the sampling tube designed to clear it efficiently; the respiratory passages were cut off from communication with the outside air during the whole process of sampling; and there were no valves through which contamination might occur. Sampling took place at the mouth itself.

Values we have recorded represent therefore the gas composition in the upper respiratory passages at the moment of sampling.

The total amount of gas we have removed is no more than is taken in larger sampling tubes for ordinary Haldane-Priestley collections. This is mentioned because at first sight it might appear that a sample is being removed from the lower respiratory tract. The volumes involved speak for themselves; the negative pressure developed in the mouth during evacuation is only in the region of 4 mm. Hg.

The procedure is, in effect, the collection of a sample of approximately 110 ml., only the last 10 ml. of which is analyzed. There is minimal disturbance of the subject.

Observations made on arterial alveolar air mixing should also apply to venous alveolar air estimations, and the technique of sampling described in this paper is being modified to estimate venous CO_2 tensions by an equilibration method.

SUMMARY

Mixing of alveolar air with respiratory dead-space air has been studied. By using a mechanical sampling apparatus, which is described, samples of

alveolar air closely approximating to Haldane-Priestley end-expiratory samples have been obtained without cooperation from the patient. These have been compared in one subject with samples collected from the end of normal expirations, and the significance of the values obtained, in relation to Haldane-Priestley estimations, have been discussed.

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Effects of Tetra-ethyl-ammonium Chloride on the Cardiovascular Reactions in Man to Changes in Posture and Exposure to Centrifugal Force

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THE SELECTIVE BLOCKADE of autonomic ganglia by the tetra-ethyl-ammonium ion was demonstrated by Acheson and Moe (1). Lyons and his associates (2) have demonstrated that the reactivity of the cardiovascular system of man is markedly affected by the tetra-ethyl-ammonium ion. The present study was carried out to elucidate the detailed effects of this drug on the various reactions associated with changes in the force environment. The continuous method of recording previously described (3) was employed. Studies were carried out on the effect of the drug on the reactions produced in the cardiovascular system by tilting from the supine to the upright position, exposure to centrifugal force, and by the sitting posture.

METHODS

Eight healthy men were chosen as subjects and tests were carried out under controlled conditions of temperature and fasting (3). A tilt table of the footboard type was used; each subject was instructed to stand quietly with the weight of the body equally distributed on both legs and to remain as relaxed as possible while the table was being tilted. A belt loosely placed about the waist assured the subject that he would not fall forward. The position of the table was recorded by means of a strain gauge accelerometer[1] as a function of the component of gravity acting from head to foot parallel with the table top.

Intra-arterial blood pressure was measured after puncture of the right

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[1] Model AF 15 ± 12 *g*.

radial artery at the wrist with a strain gauge manometer[2] of the type described by Lambert and Wood (4). The manometer and site of arterial puncture were adjusted to remain at the level of the third intercostal space at the sternal border throughout all changes in body position. Venous pressure was recorded from the greater saphenous vein at the right ankle by means of a similar manometer which was adjusted to remain in the same position in respect to the site of venipuncture during changes in position. An electrocardiogram recorded from leads placed on each side of the chest below the nipples activated an instantaneous recording cardiotachometer (5).

Intrarectal pressure was recorded from a strain gauge manometer attached to a catheter and balloon which was inserted 12 cm. above the anal ring. Respiration was recorded by use of a mouthpiece containing a thermocouple. Ear opacity (ear volume) and ear opacity pulse were recorded by photo-electric plethysmographs. Plethysmographic measurements of volume[3] of the leg were made in some subjects (7).

Continuous recordings were made during a control period of 22 to 54 minutes, at intervals during which the subject was tilted upright (70° from the horizontal) for periods of 15 seconds or 2 to 5 minutes. Tetra-ethyl-ammonium chloride was then injected into the left antecubital vein with the subject lying on his back in the horizontal position. *Subjects 1, 2* and *3* were given single injections of 5.5 to 7.7 mg/kg. of body weight slowly over a period ranging from 1.5 to 3.5 minutes. *Subjects 4* through *8* were given doses of 5.5 to 7.7 mg/kg. of body weight in five equally divided doses injected rapidly (2 to 5 seconds) at intervals of 1 to 2 minutes. When the maximal effect of the drug had been attained as indicated by observation of the effect on heart rate, the subjects were tilted upright for periods of 15 seconds or 2 to 5 minutes. The heart rate and blood pressure were allowed to stabilize before a subsequent procedure was carried out. In no instance was the interval between procedures less than 2 minutes.

Two of the subjects (*subjects 7* and *8*) were subjected to the effects of positive acceleration on the Mayo centrifuge (8). In these experiments arterial pressure was recorded simultaneously from both radial arteries. One wrist was supported at the level of the heart (third interspace at the sternum) and the other at the level of the head (external auditory meatus). During the control period each subject was exposed to accelerations of 2 to 5 *g* for periods of 15 seconds. A total dose of 7.7 mg. of tetra-ethyl-ammonium chloride per kilogram of body weight was then injected into the right antecubital vein while the subject remained seated in the cockpit of the centrifuge. The drug was injected rapidly (in 2 to 5 seconds) in five equally divided doses spaced at

[2] Model P6-15D-250 manufactured by the Statham Laboratories, Inc., Beverly Hills, California.

[3] These measurements were made with the assistance of Dr. O. H. Slaughter (6).

intervals of one minute. When the maximal effect of the drug was observed, the subjects were again exposed to the acceleration.

RESULTS

Arterial Pressure and Tilting. The sequence of events that occurred when a normal subject was tilted upright to 70° from the supine position and maintained there for 15 seconds is shown in figure 1. The responses of the cardiovascular system during tilting can be divided into two phases: a period of failure in which the arterial blood pressure at heart level decreased and a period of compensation in which some recovery of the blood pressure occurred.

During the period of failure associated with tilting upright to 70° in the control studies, the systolic blood pressure at heart level fell in all subjects, the average decrease being 20 mm. Hg less than average values recorded in the period before the tilt (table 1). The diastolic pressure was decreased in 7 of the 8 subjects and increased in one. The average decrease for all subjects was 6 mm. Hg. The lowest blood pressure occurred at an average time of 7 seconds after the full 70° tilt was attained. (An average time of two seconds was required to tilt the subject from a supine to the 70°-upright position.)

The period of compensation was observed in all subjects in the control tests. During this period the average increase in systolic pressure above the lowest level reached in the period of failure was 19 mm. Hg. The average increase in diastolic pressure was 9 mm. Hg. The compensatory recovery of arterial pressure reached its maximum on the average 12 seconds after the subject was tilted upright.

The administration of tetra-ethyl-ammonium chloride markedly affected the period of compensation as can be noted in figure 1 and in table 1. When tilting was done within 15 minutes after the injection of this drug, the period of progressive failure was prolonged so that the lowest arterial pressure occurred at an average of 12 seconds after full tilt was attained. An average decrease of 55 mm. Hg in systolic pressure and 28 mm. Hg in diastolic pressure below average values in the pre-tilt period was observed in the 8 subjects as a consequence of this prolonged period of failure. Compensatory recovery of arterial pressure was practically abolished. When studies were made at longer intervals after injection of the drug, compensatory changes in the arterial pressure again were significant as recorded in table 1. The period of failure was terminated earlier in the tilt period and the maximal decreases in pressure which occurred were progressively less marked.

When each subject was tilted back to the supine position in the control studies, there was often a brief, slight decrease followed by a sharp increase in blood pressure. The average maximal increase in systolic pressure, above the values recorded during the immediate low after the tilt, was 31 mm. Hg (range 16–52). The average change in diastolic pressure for the 8 subjects was an

increase in pressure of 3 mm. Hg (3 of the subjects had a decrease of 1–8 mm. Hg). The maximal systolic pressure after the tilt occurred on the average at 8 seconds after the table reached the horizontal position. The arterial pressure of the subjects then slowly decreased so that values approximating those recorded in the pre-tilt period were attained 25 seconds after return to the supine position.

When tilting was carried out within 15 minutes after injection of tetra-ethyl-ammonium chloride, a slight decrease in pressure usually occurred immediately after the return to the supine position but this was not followed by the sharp increase of pressure noted in the control period. Instead both systolic and diastolic blood pressures increased slowly until pre-tilt values were attained 40 seconds after the return to the horizontal position. The average changes in arterial pressure that occurred during tilting and during the period following the return to the supine position in the 8 subjects before and after the administration of tetra-ethyl-ammonium chloride are illustrated in figure 2.

In the recovery periods following periods of tilting carried out from 15 to 30 minutes after injection of the drug, the average increase in pressure was 49 mm. Hg systolic and 21 mm. Hg diastolic with the maximal pressure occurring at an average of 9 seconds after resumption of the horizontal position. The return of arterial pressure to pre-tilt values occurred in 39 seconds. When tilting was carried out from 30 to 45 minutes after the drug was given, these same values were 29 mm. Hg systolic and 8 mm. Hg diastolic with the maximal pressure at an average time of 9 seconds after return to the supine position. Blood pressure returned to the levels before tilting in 27 seconds after resumption of the supine position.

Heart Rate During Tilting. The changes of heart rate occurring when 8 normal subjects were tilted upright to 70° from the supine position also showed two distinct phases. The heart rate increased during the period of failure and slowed during the period of compensation in all subjects (figs. 1 and 3). Previous to the administration of tetra-ethyl-ammonium chloride the average maximal increase in heart rate during tilting was 20 beats per minute above the average pre-tilt rate. This maximal heart rate occurred on the average at 9 seconds after attainment of the upright position and was followed 5 seconds later by an average maximal decrease of 13 beats per minute below this level.

During maintenance of the upright position, when tilting was carried out within 15 minutes after the injection of the drug, compensatory slowing of the heart rate was not observed in any of the subjects (figs. 1 and 3). The heart rate continued to increase slightly throughout the period of the tilting. The average maximal increase in heart rate above the rate prior to tilting was 15 beats per minute.

In the period of recovery following return to the horizontal position, an immediate initial increase in heart rate was observed (fig. 3). In the control studies before any drug was given this increase was followed by prompt slow-

ing of the rate to an average of 30 beats per minute (range 16–42) less than that noted during the acceleration just mentioned. The maximal slowing occurred on the average of 7 seconds after the return to the supine position.

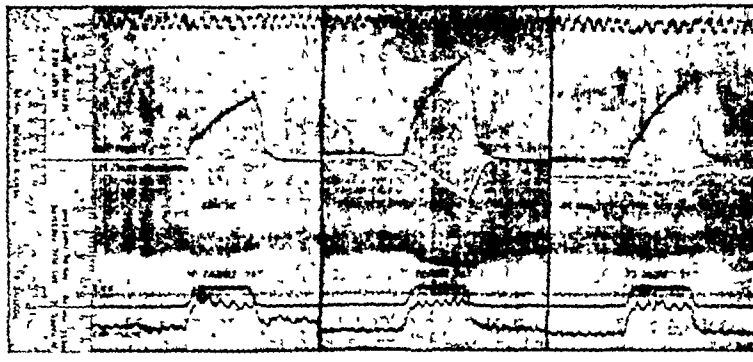

Fig. 1. PHYSIOLOGIC EFFECTS PRODUCED IN A NORMAL MAN by tilting upright to 70° from the supine position for 15 seconds before and after the intravenous injection of 7.7 mg. of tetra-ethyl-ammonium chloride per kilogram of body weight. Temporary loss of vision (blackout) occurred at the end of the period of tilting carried out 5 minutes after injection of the drug.

TABLE 1. EFFECT OF INTRAVENOUS ADMINISTRATION OF TETRA-ETHYL-AMMONIUM CHLORIDE ON CHANGES IN ARTERIAL PRESSURE AT LEVEL OF THE HEART INDUCED BY TILTING UPRIGHT TO 70° FROM THE SUPINE POSITION FOR 15 SECONDS

The changes in blood pressure in each tilt were averaged for each subject. The values presented are the average of these values. Figures in parentheses are extreme values

MIN AFTER INJECTION TEA[1]	NO OF SUBJECTS	NO OF TILTS	MAXIMAL DECREASE IN PRESSURE[2]			MAXIMAL COMPENSATORY INCREASE IN PRESSURE[3]		
			Systolic pressure	Diastolic pressure	Time of occurrence, seconds at 70° tilt	Systolic pressure	Diastolic pressure	Time of occurrence, seconds at 70° tilt
			mm Hg	*mm Hg*		*mm. Hg*	*mm Hg*	
Control	8	35	20 (7–37)	6 (−1–14)	7 (5– 8)	19 (11–36)	9 (3–16)	12 (11–13)
5–15	8	17	55 (35–80)	28 (19–44)	12 (7–14)	3 (0– 6)	2 (1– 6)	13 (11–15)
15–30	8	18	43 (24–76)	19 (8–34)	8 (5–11)	15 (9–26)	11 (6–14)	13 (11–15)
30–45	6	14	29 (17–47)	11 (7–15)	9 (7–14)	20 (6–32)	11 (0–25)	12 (10–13)

[1] Total dose of drug 5.5–7.7 mg/kg of body weight.

[2] Average pressure during 15 seconds prior to tilting minus minimal pressure during tilting; a negative number indicates an increase.

[3] Maximal pressure during compensation minus minimal pressure during failure.

The heart rate then returned to the control level at an average time of 29 seconds after resumption of the horizontal position. The immediate recovery phase when tilting was carried out within 15 minutes after injection of the drug differed significantly from this control sequence (figs. 1 and 3). The slight

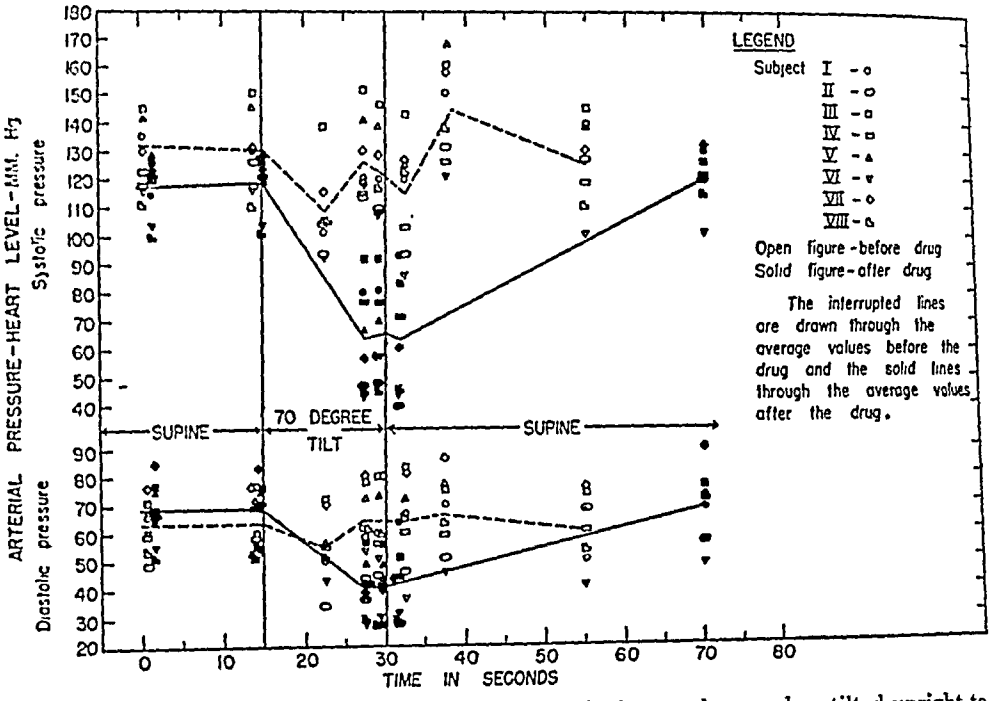

Fig. 2. AVERAGE CHANGES IN ARTERIAL PRESSURE in 8 normal men when tilted upright to 70° from the supine position for 15 seconds before and within 15 minutes after intravenous injection of tetra-ethyl-ammonium chloride. The total dose of the drug ranged from 5.5 to 7.7 mg/kg. of body weight.

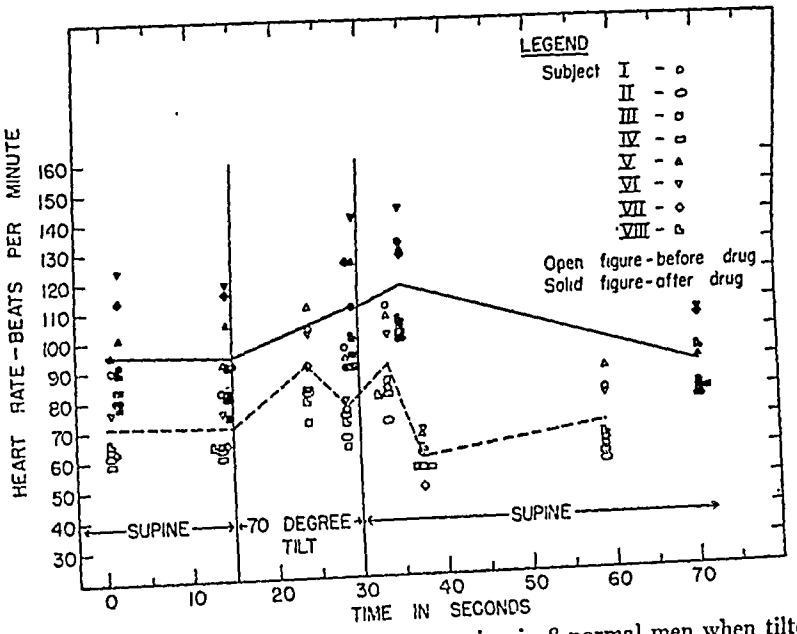

Fig. 3. AVERAGE CHANGES IN HEART RATE occurring in 8 normal men when tilted upright to 70° for 15 seconds before and within 15 minutes after intravenous injection of tetra-ethyl ammonium chloride. The total dose of the drug ranged from 5.5 to 7.7 mg/kg. of body weight.

further increase in rate immediately after return to the supine position was observed. However, a subsequent prompt slowing in rate was not observed in any subject. Rather, the heart rate decreased slowly so that the pre-tilt values were regained at an average time of 41 seconds after return to the supine posi-

tion (figs. 1 and 3). The average changes in heart rate produced by tilting to 72° for 15 seconds are given in table 2.

Other Variables During Tilting. Venous pressure in the greater saphenous vein at the ankle increased progressively throughout each 15-second period of tilting carried out on 5 normal subjects (table 3). The average increase in venous pressure at the end of 15 seconds in the upright position was 35 mm. Hg previous to the injection of tetra-ethyl-ammonium chloride and was 50 mm. Hg when tilting was carried out within 15 minutes after administration of this drug. The increase in venous pressure at the ankle during tilting for 15 seconds was progressively less as the interval between the administration of the drug and the tilting increased (fig. 1).

TABLE 2. EFFECT OF INTRAVENOUS INJECTION OF TETRA-ETHYL-AMMONIUM CHLORIDE ON THE CHANGES IN HEART RATE INDUCED BY TILTING UPRIGHT TO 70° FROM THE SUPINE POSITION FOR 15 SECONDS

The values presented are the averages of each subject's average. Figures in parentheses are extreme values.

MIN. AFTER INJECTION TEA[1]	NO. OF SUBJECTS	NO. OF TILTS	MAXIMAL INCREASE IN HEART RATE[2]		MAXIMAL COMPENSATORY DECREASE IN HEART RATE[3]	
			Beats/min.	Time of occurrence, seconds at 70° tilt	Beats/min.	Time of occurrence, seconds at 70° tilt
Control	8	35	20 (6–30)	8.9 (5–12)	13 (6–23)	13.6 (12–15)
5–15	8	17	15 (7–23)	14.8 (14–15)	None	—
15–30	8	18	20 (8–31)	14.1 (9–15)	1 (0– 7)	14.5 (12–15)
30–45	6	14	16 (13–23)	12.0 (10–15)	3 (0– 7)	13.7 (12–15)

[1] Total dose of the drug was 5.5–7.7 mg/kg. of body weight.
[2] Maximal rate during tilting minus average rate during 15 seconds prior to tilting.
[3] Maximal rate during failure minus minimal rate during compensation.

When the 70° upright position was maintained for 2 to 5 minutes (fig. 4), the venous pressure continued to increase until it reached a plateau at an average value of 89 mm. Hg. After this plateau was attained, slight variations synchronous with respiration were noted consistently to occur (fig. 4). The plateau pressures before and after the injection of tetra-ethyl-ammonium chloride were not significantly different and were sufficient to support a column of blood from the ankle up to approximately the level of the third interspace at the sternum. The drug, however, significantly decreased the time required for re-establishment of venous return from the feet (fig. 4). During control studies the time after tilting required for the venous pressure to increase to the plateau value averaged 55 seconds and ranged from 50 to 60 seconds. When tilting was carried out within 30 minutes after the drug was given, the average time required was 23 seconds with a range of from 15 to 30 seconds.

The changes in volume of the leg (recorded for 5 subjects) paralleled the changes in venous pressure (fig. 1). In the control studies, the average increase in volume of the leg at the end of 15 seconds in the upright position was 49 cc. (air displaced from the plethysmograph). When tilting was carried out within 15 minutes after injection of tetra-ethyl-ammonium chloride (table 3), the average increase in volume of the leg during the 15-second period of tilting was 65 cc. The apparatus employed to measure changes in volume of the leg did not allow accurate measurements to be made of some of the larger increases in volume which occurred when the subjects were tilted upright for periods of 3 minutes. It is of interest, however, that the values which were obtained

TABLE 3. EFFECT OF INTRAVENOUS TETRA-ETHYL-AMMONIUM CHLORIDE ON THE CHANGES IN VENOUS PRESSURE AT THE ANKLE AND IN VOLUME OF THE LEG INDUCED BY TILTING UPRIGHT TO 70° FOR 15 SECONDS

The values presented are the averages of each subject's averages. Figures in parentheses are extreme values.

MIN. AFTER INJECTION TEA[1]	NO. OF SUBJECTS	NO. OF TILTS	AVERAGE INCREASE WHEN TILTED FOR 15 SECONDS			
			In venous pressure[2]		In volume of leg[3]	
			In mm. Hg.	In mm. Hg. per second	In cc.	In cc. per second
Control	5	23	35 (27–48)	2.3 (1.8–3.2)	49 (29–86)	3.6 (1.9–5.7)
5–15	5	12	50 (34–74)	3.3 (2.3–4.9)	65 (39–91)	4.4 (2.6–6.3)
15–30	5	11	48 (30–66)	3.2 (2.0–4.4)	69 (35–106)	4.6 (2.3–7.2)
30–45	5	13	45 (23–64)	3.0 (1.5–4.3)	72 (39–109)	4.8 (2.6–7.8)

[1] Total dose of the drug was 5.5 to 7.7 mg/kg. of body weight.

[2] Venous pressure 15 seconds after full tilt was attained minus venous pressure during 15 seconds prior to tilt.

[3] Volume of leg was measured in cubic centimeters of air displaced from plethysmograph after the subject was tilted upright. The plethysmograph enclosed the leg and foot below the knee.

(average 90 cc. with a range of 46 to 122 cc.) were roughly the same before and after the injection of tetra-ethyl-ammonium chloride. This suggests that although the rate of filling of the leg (blood flow) was increased, the volume of blood ultimately displaced into the leg (pooling) was not increased by tetra-ethyl-ammonium chloride.

The blood content of the ear (ear opacity) decreased in all subjects when they were tilted upright to 70°. The decrease was slight and occurred in association with the fall of arterial pressure during the period of failure. Some recovery of the blood content occurred during the period of compensation (fig. 1). Following the injection of tetra-ethyl-ammonium chloride the blood content of the ear decreased progressively throughout the 15-second period of tilting. During tilting of longer duration (fig. 4), slight compensatory increases in vol-

ume were observed but in no instance did the volume of the ear return to a level approximating that before tilting.

The changes in rectal pressure produced by tilting were unaffected by the injection of tetra-ethyl-ammonium chloride though the spontaneous waves

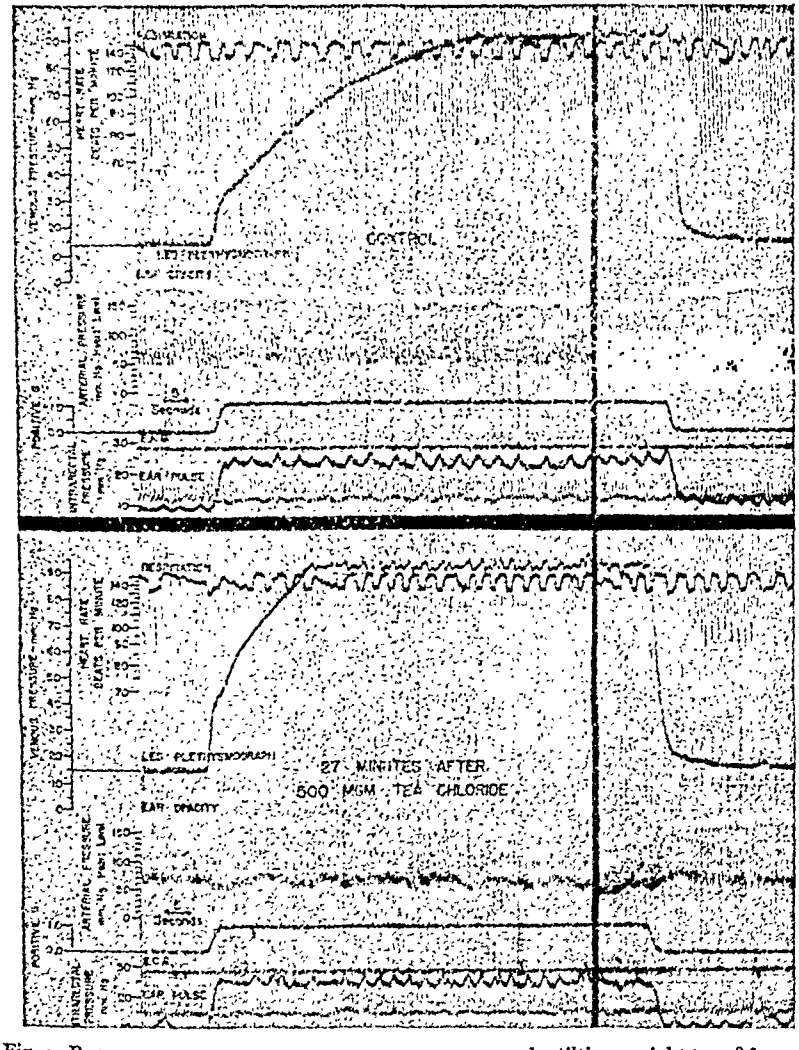

Fig. 4. PHYSIOLOGIC EFFECTS PRODUCED IN A NORMAL MAN by tilting upright to 70° for 3 minutes before and after intravenous injection of 7.7 mg. of tetra-ethyl-ammonium chloride per kilogram of body weight.

often observed were obliterated (fig. 1). The average maximal increase in rectal pressure in 5 subjects was 12.4 mm. Hg during tilts before the drug was given and 13.3 mm. Hg during tilts within 30 minutes after injection of the drug.

Comparative Effects of the Drug on Subjects in the Supine and Seated Positions. The intravenous injection of 7.7 mg. of tetra-ethyl-ammonium chloride

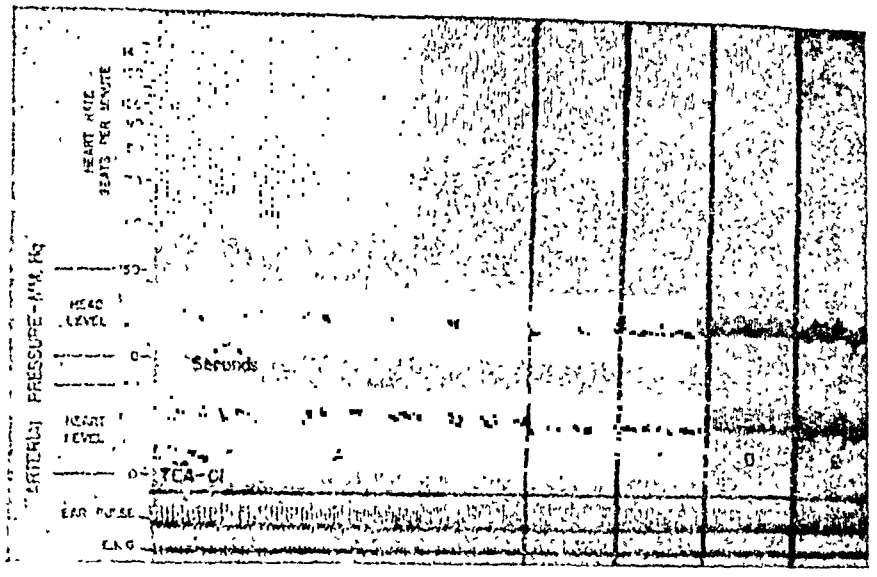

Fig. 5. PHYSIOLOGIC EFFECTS PRODUCED IN A NORMAL MAN in the sitting position by 5 successive intravenous injections of 1.54 mg. of tetra-ethyl-ammonium chloride per kilogram of body weight (total dose 7.7 mg/kg.). Each dose was injected in a period of 2 to 3 seconds. An interval of 120 seconds elapsed between the first and second doses and an interval of 60 seconds between the subsequent doses. Panel *A* shows the immediate effects of the first injection, panels *B*, *C*, *D* and *E* were recorded during the period from 45 to 60 seconds after injection of the second, third, fourth and fifth doses, respectively.

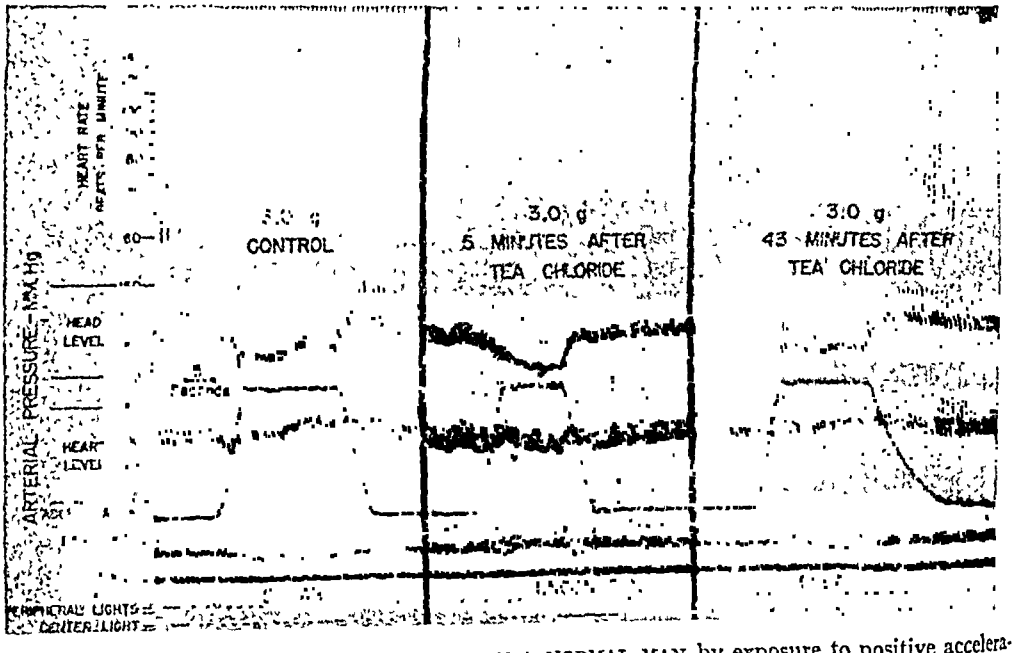

Fig. 6. PHYSIOLOGIC EFFECTS PRODUCED IN A NORMAL MAN by exposure to positive acceleration (centrifugal force) before and after intravenous injection of 7.7 mg. of tetra-ethyl-ammonium chloride per kilogram of body weight.

per kilogram of body weight into 2 subjects in the seated position was followed in each instance by a decrease in systolic and diastolic blood pressure and acceleration of the heart (fig. 5).

A comparison of these changes with the changes produced by the same dose of the drug while these subjects were in the supine position is of interest.

In both subjects, the maximal decrease in systolic pressure after administration of the drug below the average pressure in the control period was greater when they were in the sitting position. However, the pressure in the control period before administration of the drug was higher when the subjects were seated than when they were supine. Consequently the percentage decrease in systolic pressure produced by the drug was not significantly different, for it averaged 25 per cent in both the seated and the supine positions. In these 2 subjects the average maximal increase in heart rate produced by the drug was 47 per cent when they were seated as compared to the 29 per cent when they were supine.

Effects of the Drug on the Cardiovascular Reactions Produced by Exposure to Centrifugal Force. By its ability to block the compensatory reflexes normally induced by exposure to positive acceleration, tetra-ethyl-ammonium chloride markedly altered the reactions of the cardiovascular system produced by this change in the force environment.

These alterations in the cardiovascular responses and consequent change in tolerance to positive acceleration are illustrated in figure 6. Before injection of the drug the subject maintained clear vision and responded promptly to light signals throughout a 15-second exposure to 3 *g*. The maximal decrease of arterial blood pressure occurred after 5 seconds of exposure to 3 *g* had elapsed. The maximal compensatory increase in arterial pressure occurred 12 seconds after the onset of the exposure. Changes in heart rate approximately mirrored the alterations in blood pressure. Repetition of the exposure to 3 *g* 5 minutes after injection of 7.7 mg. of tetra-ethyl-ammonium chloride per kilogram of body weight produced a much greater decrease in blood pressure. These changes in blood pressure failed, however, to produce appreciable effects on the heart rate. The period of failure was not interrupted by compensatory reflexes so that arterial pressure continued to decrease throughout the exposure. Consciousness was lost after the pressure at head level had been reduced to zero for approximately four seconds. Maximal acceleration was terminated in 9 seconds from onset and the subject recovered promptly. The reactions produced by an exposure to 3 *g* 43 minutes after the injection of tetra-ethyl-ammonium chloride were similar to those induced by the exposure which preceded the administration of tetra-ethyl-ammonium chloride.

The changes in blood pressure at the level of the heart and of the head produced in 2 subjects by exposure to centrifugal force in a human centrifuge before and after intravenous injections of tetra-ethyl-ammonium chloride are summarized in table 4. The compensatory increase in systolic pressure which occurred during exposure and which ranged from 30 to 66 mm. Hg in the control tests was practically abolished during the 6 minutes immediately following injection of the drug. In the period from 14 to 43 minutes after injection of the drug this reaction reappeared so that the compensatory increase in systolic pressure during acceleration ranged from 18 to 50 mm. Hg.

In the 2 subjects the maximal increase in heart rate produced by exposure to acceleration before the drug was administered occurred on the average at 7 seconds after the onset of the exposure. This was 2 seconds after the maximal decrease in blood pressure had occurred. The maximal compensatory decrease in heart rate occurred on the average at 12 seconds (one second after the maximal compensatory increase in arterial pressure). When these subjects were exposed to the same acceleration within 6 minutes after the injection of tetra-ethyl-ammonium chloride, the period of decrease in systolic blood pressure was prolonged. The maximal increase in heart rate occurred 14 seconds

TABLE 4. EFFECT OF INTRAVENOUS TETRA-ETHYL-AMMONIUM CHLORIDE ON THE CHANGES IN ARTERIAL PRESSURE AT HEAD AND HEART LEVELS INDUCED BY EXPOSURE TO CENTRIFUGAL FORCE[1]

SUBJECT	POSITIVE ACCELERATION g UNITS[1]	MINUTES AFTER INJECTION TEA[2]	MAXIMAL DECREASE IN ARTERIAL PRESSURE, MM. HG[3]					MAXIMAL COMPENSATORY INCREASE IN ARTERIAL PRESSURE MM. HG[4]				
			Heart level		Head level		Seconds after onset of max. g	Heart level		Head level		Seconds after onset of max. g
			Systolic	Diastolic	Systolic	Diastolic		Systolic	Diastolic	Systolic	Diastolic	
5	3.0	Control	0	−13	58	35	5	42	16	38	18	10
		2	20	3	75	47	14	0	0	0	0	—
		18	6	−11	58	38	5	32	12	30	16	10
	4.0	Control	11	−5	99	55	3	62	36	66	26	9
		4	21	−7	103	64	13	16	2	10	0	14
		14	21	−1	109	61	4	46	30	50	20	10
8	2.5	Control	2	−7	58	32	5	42	12	50	12	12
		6	35	11	65	40	14	0	0	0	0	—
		42	16	6	51	29	5	30	22	34	18	13
	3.0	Control	13	−3	58	34	5	30	14	40	12	12
		5	32	14	76	47	9	0	0	0	0	—
		43	−3	−9	54	32	5	18	14	20	10	14

[1] The exposures to centrifugal force were 15 seconds in duration.

[2] The dose of tetra-ethyl-ammonium chloride was 7.7 mg/kg. of body weight.

[3] Average pressure during 15 seconds prior to acceleration minus minimal pressure during acceleration; negative numbers indicate an increase.

[4] Maximal pressure during compensation minus minimal pressure during failure.

after maximal acceleration was attained and no compensatory slowing of the rate was observed. Exposures to the same force at intervals of time exceeding 14 minutes after injection of the drug were accompanied by compensatory cardiac decelerations similar to those produced prior to administration of the drug.

COMMENT

The consequences in man of exposure to acceleratory forces acting in the direction of head to foot (positive acceleration) are due largely to the effects of increased hydrostatic pressure in the vascular tree. The immediate effects on the cardiovascular system are similar qualitatively whether they are due to

the action of gravity when man changes from a lying to an upright or sitting position, or whether they are due to the action of forces of greater magnitude generated by centrifugation. Striking cardiovascular adjustments to a change in the force environment occur within the first 15 seconds of the exposure. These adjustments are directed at maintaining arterial pressure at the level of the head and blood flow through the brain.

In 1895, Hill (7) recognized the perfection of the compensating mechanisms existing in man and monkeys that enable these animals to withstand the effects of gravity produced by the upright position in which they were destined to exist. Subsequent studies, such as those conducted by Mayerson (9) and Greenfield (10), have demonstrated that the compensatory responses are initiated by changes in arterial pressure in the carotid sinuses and aortic arch and are mediated reflexly through the autonomic nervous system. Arterial vasoconstriction is induced in this manner and arterial blood pressure is sustained to a degree that insures adequate cerebral circulation. After section of the nervous pathways of these reflexes in dogs, a fall of arterial blood pressure occurs when the animals are tilted to the head up position (9).

Wood and his associates (11) in studies carried out in human beings exposed to positive acceleration in the human centrifuge showed that a delay of 5 to 12 seconds occurred between the exposure to the changing force environment and the occurrence of effective compensation as indicated by a beginning recovery of arterial pressure after its initial fall at head level. The present study, in which human subjects were tilted erect to 70°, revealed a similar delay, averaging 7 seconds, before the appearance of compensation. As in the studies carried out on the human centrifuge (11), the present investigation demonstrates that the changes recorded in the cardiovascular system are clearly differentiated into two phases. Initially, a period of failure characterized by a fall in arterial blood pressure at heart level and at head level was accompanied by acceleration of the heart. These events were terminated by an increase in arterial blood pressure and a subsequent slowing of the heart rate during the period of compensation. It is of interest that the effects of 3 and 4 *g* on the arterial pressure at heart level of a subject in the sitting position in the human centrifuge were less marked than the effects of 1 *g* on the subjects studied on the tilt table. However, the effect of the former on arterial pressure at head level was considerably greater than the latter because of the greater accelerative force acting on the arterial column between the heart and head. In both instances it is probable that the change in pressure at head level (carotid sinus) is most important in initiating the compensatory cardiac reflexes which occur.

Tetra-ethyl-ammonium chloride has been shown by Acheson and Moe (1) to have as its chief action the ability to block the transmission of nerve impulses through sympathetic and parasympathetic ganglia. Because of this blocking action, the drug abolishes reflex responses mediated through the auto-

nomic nervous system. Thus in subjects exposed to centrifugal force or tilted from the supine to upright positions, peripheral vasoconstriction which has been shown to be the chief compensating mechanism responsible for maintaining an adequate cerebral blood flow is abolished. As a consequence, the period of failure with continuing fall of arterial blood pressure produced by the upright position or exposure to positive acceleration is prolonged when exposure occurs within 15 minutes after injection of the drug, that is, during the period when its blocking effect is most complete. In studies carried out during intervals of more than 15 minutes after administration of the drug, these effects were less pronounced for the fall of arterial pressure is terminated by the reappearance of some degree of compensation. The fall in arterial blood pressure, however, continues to be greater than the control for periods of more than 30 minutes after injection of the drug (table 1). This is in accord with the findings of Hoobler and his associates (12) who noted the persistence of orthostatic hypotension for as long as 45 minutes after administration of tetra-ethyl-ammonium chloride.

When the period of tilting was prolonged to two or more minutes in the control tests before injection of the drug, an interval of time averaging 55 seconds elapsed before venous pressure at the ankle reached a plateau. At the plateau the pressure was found to be equal to the hydrostatic pressure of a column of blood reaching from the ankle to approximately the third intercostal space. This was considered evidence that the column of venous blood at this moment was reaching the base of the heart. In spite of the delay of 55 seconds before the venous pressure leveled off and thus a similar delay in the return of venous blood to the heart from the lower part of the leg, the fall of arterial blood pressure was terminated at an average time of 7 seconds after tilting by a compensatory response. After the intravenous injection of tetra-ethyl-ammonium chloride, the venous pressure reached the plateau level within an average time of 23 seconds; this period indicates more rapid filling of the vessels of the leg and earlier return of venous blood to the heart. The failure of compensation as indicated by a continued decrease in arterial blood pressure following injection of the drug, therefore, cannot be ascribed solely to an inadequate return of venous blood to the heart.

An increase in the volume of the leg and foot has been shown to occur when normal human subjects are tilted to the 70° erect position from the supine position. The increase in volume of the leg within 15 seconds after tilting is greater following the injection of tetra-ethyl-ammonium chloride than when this drug has not been given. The more rapid increase in volume of the leg together with the more rapid rise of venous pressure at the ankle is evidence that blood flow to the dependent parts of the body was increased by the drug. The observations made in these studies are in harmony with the concept that

the increased flow of blood to the dependent parts is the primary factor in the production of the greater fall of arterial pressure during exposure to positive acceleration or the erect position after injection of tetra-ethyl-ammonium chloride. The volume of venous blood returned to the heart probably is not less, but greater than that returned to the heart in the upright position before injection of the drug.

However, relative to the capacity of the heart to utilize venous blood required for the increased cardiac output necessary for the maintenance of arterial pressure after the injection of tetra-ethyl-ammonium chloride, the venous return may be inadequate. Nevertheless, there is no evidence to suggest that this is the primary deficiency responsible for the decreased tolerance to positive acceleration and postural hypotension produced by the drug. It may be a limiting factor, however, in man's ability to compensate for the loss of reflex vasoconstriction following the interruption of reflex pathways by the autonomic ganglionic blockade effected by the tetra-ethyl-ammonium ion (13, 14).

CONCLUSIONS

Studies of man's reactions to the effects of gravity produced by tilting erect to 70° from the supine position or by exposure to positive acceleration (centrifugal force) reveal that a fall in arterial blood pressure and an increase in heart rate result. These physiologic effects are quickly compensated for by reflex mechanisms mediated by the autonomic nervous system which produce an increase in arterial pressure at heart level and a subsequent slowing in heart rate.

The intravenous injection of 5.5 to 7.7 mg. of tetra-ethyl-ammonium chloride per kilogram of body weight has been found to block these reactions for periods of 5 to 15 minutes so that arterial pressure continues to fall often to levels that produce symptoms of cerebral anoxemia. The marked decreases in arterial pressure fail under these circumstances to produce compensatory alterations in heart rate. The compensatory cardiovascular reactions induced by tilting to an upright position of 70° or exposure to centrifugal force are gradually recovered in a period of from 10 to 45 minutes after injection of the drug.

Simultaneous studies of arterial pressure, heart rate, venous pressure and volume of the leg indicate that these compensatory reactions which determine man's tolerance to the upright position or positive acceleration are chiefly concerned with the arterial rather than the venous side of the circulation. The failure of reflex vasoconstriction to compensate for the increased hydrostatic pressure in the dependent parts of the body and thus to prevent an increase in blood flow through these parts, rather than reduced venous

return to the heart, is the primary factor accounting for the reduction of man's tolerance to positive acceleration after the administration of tetra-ethyl-ammonium chloride.

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Cerebral Dysfunction During Negative Acceleration

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NEGATIVE ACCELERATION[3] is the term applied to acceleration in the head to heart direction. This results in a force of inertia tending to force the blood and other body components toward the head. It is this headward centrifugal force that the pilot encounters in such maneuvers as an outside loop or turn. On a human centrifuge the subject experiences negative acceleration if his body is so positioned that the axis of the trunk is directed radially with the head away from the center of rotation.

The studies undertaken by Jongbloed and Noyons (1) to determine the effects of headward centrifugal force on the circulatory system remain the classical work in this field. These investigators in 1933, working with rabbits on a small turntable, noted a dramatic bradycardia at 2½ g and demonstrated by denervation of the carotid sinus that it was due to increased pressure in the carotid artery with a resulting carotid sinus reflex response and vagal stimulation. Five years later, Armstrong and Heim (2) subjected men to negative acceleration on one of the first human centrifuges and described facial pain and conjunctival hemorrhages. A staggering gait and mental confusion were noted in one subject following exposure to 4 negative g for approximately 30 seconds to one minute. During the War, Ryan, Kerr and Franks (3) studying electrocardiograms taken on human subjects during exposures to 3 negative g on a centrifuge, recorded a marked bradycardia and frequent occurrence of heart block and asystole. In one case, the period of asystole was of 9 seconds' duration. They concluded that the changes were indistinguishable from those obtained when pressure is applied over a sensitive carotid sinus. Conjunctival hemorrhages are frequently observed in pilots following exposure to headward centrifugal force, and it has been suggested that confusion and unconsciousness occur (4). Anatomical studies at Wright Field and the University of Southern California (5) have revealed petechial hemorrhages and subcutaneous extravasation of blood in the soft extracranial tissues about the heads of animals following exposures to negative acceleration. These hemorrhages are assumed to be due to the markedly elevated venous pressure that is developed during the application of headward centrifugal force. However, no anatomical abnormalities have been found to explain any cerebral dysfunction. Jasper and Cypriani (6) subjected cats to multiple 10-second exposures to −4 g, following which exposures microscopic sections of the brains were prepared. No abnormalities of the blood vessels, glia, or neurons were found. Motion pictures of the blood vessels on the sur-

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[3] Negative acceleration has been used by physiologists to describe not deceleration but a force of inertia acting in the heart to head direction. In order to conform with this current usage, it is employed in this sense in the present paper.

face of a monkey brain photographed through a Forbes window at −4 *g* at Montreal (6) and through a lucite calvarium at −7 *g* at Wright Field (7) showed no changes in the caliber of the vessels during the acceleration. Recently Rushmer, Beckman and Lee (8) using cats demonstrated roughly parallel and simultaneous increases in the carotid artery, jugular vein and cerebrospinal fluid pressures during applications of negative acceleration. They concluded that there was little tendency for the blood to burst vessel walls within the skull during negative acceleration.

This report presents evidence that severe disturbances of the cerebral blood supply can occur during negative acceleration as a result of the intense stimulation of the carotid sinus zone and that unconsciousness occurring during such acceleration may therefore be of reflex origin, and not due to cerebral vascular damage.

METHODS

Human electrocardiograms were taken during negative acceleration using the Sanborn Viso-Cardiette. When this instrument was mounted at the center of the centrifuge, it was possible for the observer to visualize the tracings as they were recorded and to stop the centrifuge if necessary. The electrodes were taped directly on the body, one placed at the sternal notch and the other over the apical impulse (modified Lead II).

Blood pressures were recorded in 6 human subjects by using the Gauer-Wetterer Pressure Capsule (7). A small glass chamber was especially constructed to fit on the end of an intravenous needle and to enclose the pressure capsule. This chamber was filled with normal saline solution containing 0.5 mg. heparin/cc., which served to transmit the intravascular pressure directly to the pressure sensitive element which was then located but a few centimeters from the puncture. The venous pressure changes in the head were measured by using the frontal vein in the forehead. As there is no available artery in the head, the radial artery at the wrist was used, the wrist being held at head level directly in front of the eyes. A Lindemann type cannula (9) was used for the arterial and venous pressures.

Monopolar electroencephalograms were taken from an unanesthetized rabbit using the Grass electroencephalograph. A victrola needle, penetrating the parietal bone, 5 mm. to the left of the midline, served as one electrode, with a subcutaneous needle at the base of the ear serving as the other. With the same instrument, electrocardiograms were taken from dogs anesthetized with pentobarbital sodium (20–28 mg/kg.) using subcutaneous needles as electrodes. The first was inserted at the sternal notch and the second over the apical impulse (mod. Lead II).

Arterial and venous pressures in the dogs were recorded directly from catheters placed in the carotid artery and jugular vein. These recordings were end pressures and the vessels were ligatured around the catheters. The pressure sensitive element was the Trimount Instrument Company's type 'N' variable

inductance gauge (10). The dog's head was firmly attached to the cradle in which he was fixed, and the pressure gauges were mounted in a position over the base of the animal's skull. Thus pressures were recorded from a point approximately at the level of the carotid sinus. Pentobarbital sodium was used as a general anesthetic except where the sensitivity of the carotid sinus was being studied, when alpha chloralose was used.

RESULTS

Human Subjects. The subjects were exposed to negative acceleration while lying on their sides with the head and trunk directed away from the center of rotation. The legs were maintained at right angles with the trunk and thus were in a neutral position, transverse to the acceleration. Five subjects were given 2 to 6 exposures to -3 *g* for 15 seconds with intervals of at least 3 minutes between runs. During the acceleration there was a moderately uncomfortable fullness and tension about the head but there was no actual pain. The sensation

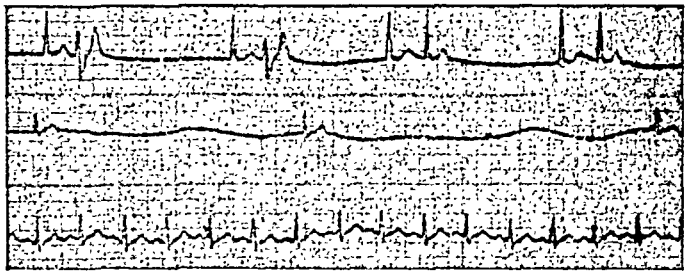

Fig. 1. ELECTROCARDIOGRAMS FROM 2 HUMAN SUBJECTS. *Upper, Subject 1,* exposed to -2.5 *g* for 15 sec.: AV nodal rhythm with ectopic beats; *Middle, Subject 2,* -3 *g* for 15 sec.: slow AV nodal rhythm with extrasystole; *Lower, Subject 2,* control.

can be simulated by assuming a head-down position on the tilt-table and superimposing a Valsalva maneuver with moderate force. Multiple small petechial hemorrhages were frequently observed in the conjunctivae, but only occasionally did actual subconjunctival extravasations of blood occur. Transient diplopia, lasting for a few minutes, was experienced twice and was then associated with mild peri-orbital edema. It is probable that the visual disturbance was due to a temporary muscular inbalance induced by the swelling of the tissues in the orbital fossae.

Electrocardiographic tracings and continuous recordings of arterial and venous blood pressures were taken from 6 subjects during exposures to -3 *g* for 15 seconds.

In figure 1 representative sections are shown of 2 electrocardiograms (mod. Lead II), taken during exposure of two subjects to $2\frac{1}{2}$ and 3 negative *g*, respectively. The records show changes of the type reported by Ryan *et al.* (3) and confirm their observation of marked vagal stimulation during negative

acceleration. The control record is placed at the bottom of the figure. It may be compared with the first record in which, during acceleration, the *P*-wave has disappeared and an AV nodal rhythm has developed. In this record there is coupling of a normal ventricular beat with a beat from ectopic focus as well as a coupling of nodal complexes. In the second, there appeared a slow AV nodal rhythm. The single notch occurring between the second and third complex is probably an abortive extrasystole. In both cases, with the end of acceleration there was a gradual resumption of a normal rhythm. All of the 6 subjects studied showed similar electrocardiographic changes although they were not all as marked as in the cases presented here. None showed carotid sinus hypersensitivity when tested by direct external pressure on the sinus.

The blood pressure recordings from these subjects indicated a rise of venous pressure of from 70 to 90 mm. Hg. The average increase in arterial pressure during the acceleration was of the same order. In most cases in this

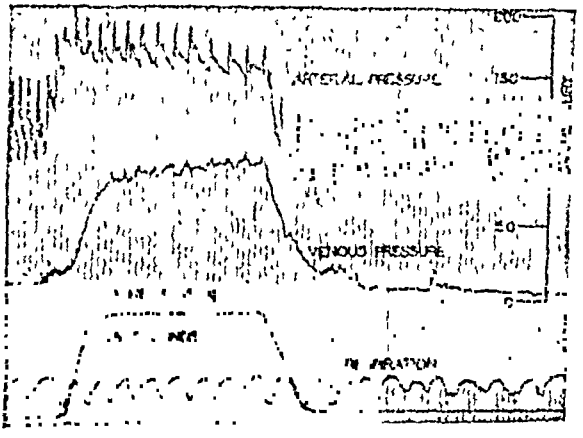

Fig. 2. SIMULTANEOUS PRESSURE RECORDINGS from radial artery at head level and from a frontal vein in the forehead; human subject exposed to −3 *g* for 15 sec.

group of experiments, only a slight decrease in the heart rate occurred. However, in 2 subjects a definite bradycardia was present. Figure 2 is a continuous recording taken from one of these and it will be seen that, although initially there was a rapid parallel rise of the arterial and venous pressures, as the run progresses the heart rate slows and there is a diminution of the arterial pressure and a steady rise in the venous pressure which may be due to a continued drainage of blood from the legs (10). Thus the arterio-venous pressure differential across the brain decreases with increasing time of application of the acceleration.

Note that the longest time between heart beats is but 1½ seconds. No recording was made of the arterial pressure change during the longer periods of asystole demonstrated in the electrocardiographic studies.

Animal Subjects. Electrocardiograms were made and blood pressure studies were undertaken in dogs to gain further knowledge of the physiological changes occurring during negative acceleration.

Inkwriter electrocardiograms (mod. Lead II) were taken during a series

of long exposures to -7 g, each lasting 2 minutes. The most dramatic effect was a pronounced bradycardia which began 3 seconds after the onset of the negative acceleration. Periods of asystole as long as 10 to 20 seconds and heart block of varying degrees with nodal and ventricular escape were noted. Extrasystoles alternating with normal complexes and a completely regular idioventricular rhythm also were recorded. In 3 dogs it was found that such changes could be abolished following section of the vagus nerve.

In 3 animals in which pressure measurements were made at the level of the carotid sinus, the arterial pressure in the carotid artery rose from the order of 100 mm. Hg to 260, 270, and 220 mm. Hg, respectively, while that in the jugular vein rose to 90, 130 and 80 mm. Hg, respectively.

Figure 3 is from the records of an experiment designed to demonstrate the effect on arterial pressure of long periods of asystole. A dog was selected which exhibited marked bradycardia when submitted to negative acceleration,

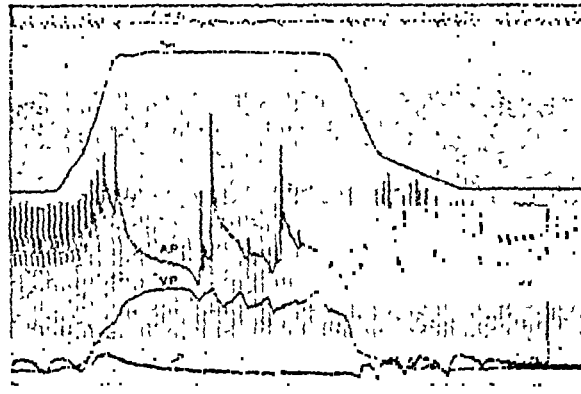

Fig. 3. SIMULTANEOUS ELECTROCARDIOGRAPHIC, arterial and venous blood pressure recordings in a dog under alpha chloralose anesthesia exposed to -5 g before vagotomy. (Vertical timing lines, $\frac{1}{5}$ second intervals. Arterial and venous pressure scales at right.)

and then alpha chloralose anesthesia was used for narcosis because this drug does not depress carotid sinus activity as does pentobarbital sodium. The record taken during an exposure to -5 g, described during each 5- to 6-second period of asystole a precipitous fall of the arterial pressure to the venous level, reducing the arterio-venous pressure differential to almost zero. The second recording, figure 4, was taken from the same dog immediately following sectioning of the vagus nerve. The bradycardia is no longer present, the arterial pressure does not fall and an adequate arterio-venous pressure differential is maintained. The same phenomenon was observed in 2 other dogs anesthetized with pentobarbital sodium.

To gain further information of the effect of negative acceleration on the central nervous system, monopolar electroencephalograms were taken from 4 unanesthetized rabbits following exposure to -7 g for one minute.

The control readings exhibited the normal pattern with large variations both in voltage and in the frequency of the waves. The predominant frequencies,

varying between 10 to 20 per second, were interspersed with bursts of more rapid activity. Immediately following the exposure, some recordings showed a regular 6 to 8 per second voltage rhythm. Reversion to the normal pattern was delayed for 15 to 30 minutes. Large, smooth, slow waves, which can be seen in figure 5 were sometimes observed. They had a frequency of approximately 1 per second and occurred immediately after exposure. It is probable

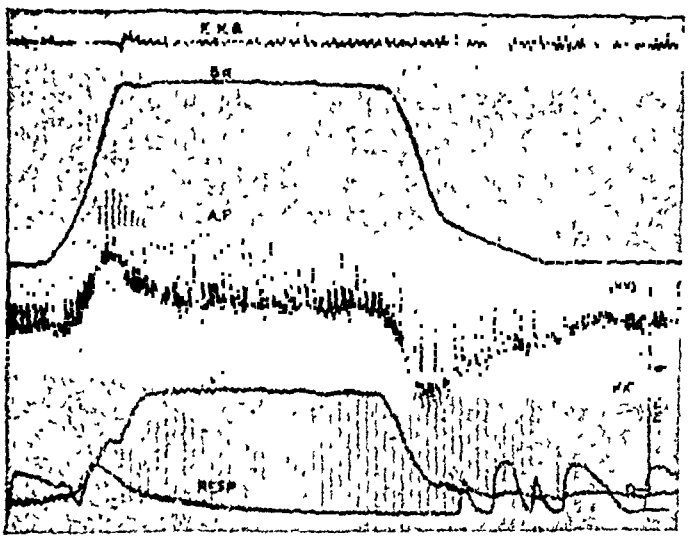

Fig. 4. RECORDINGS AS IN FIG. 3 *after* vagotomy. Arterio-venous pressure differential is well maintained. Electrocardiogram was not recorded for the first 10 seconds of the run.

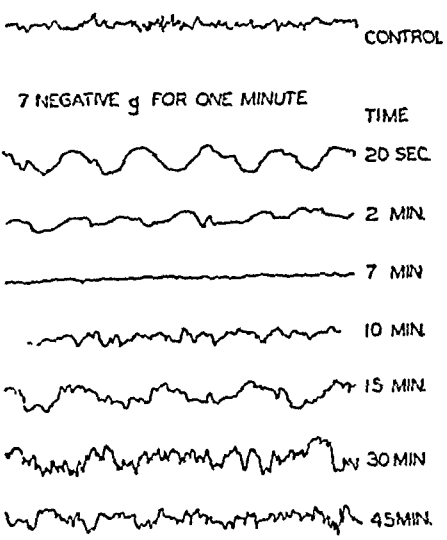

Fig. 5. ELECTROENCEPHALOGRAMS from a rabbit before and at intervals following −7 *g* for 1 min. Time of each recording, approximately 13 sec.

that these waves were of intracranial origin and represent a Delta rhythm indicative of brain injury. They are similar to those observed by Goodwin, Lloyd and Hall (11) in rabbits in hypoglycemic shock. The first evidence of recovery was a diminution of the intensity of these slow components, then after several minutes the normal rhythm returned. Repeated exposures to acceleration after a 15-minute rest period had a cumulative effect, depressing the

frequency and voltage even further. In one of the 4 animals given 4 consecutive exposures, all activity was extinguished and death occurred following the last run.

DISCUSSION

Most of the changes occurring during or immediately following negative acceleration are due to increased arterial and venous pressures as the blood is forced to the head. Jongbloed and Noyons (1) have conclusively demonstrated that in rabbits the reflex effects of the elevated cephalic vascular pressures are due to stimulation of the carotid sinus zone and the resulting vagal discharge. Such vagal stimulation could account for the bradycardia, the long periods of asystole and the heart block with resulting nodal and ventricular rhythms. Figure 2 from the human subjects suggests that falling arterial pressure is associated with the bradycardia. Figure 4 from the dogs demonstrates during a period of asystole a collapse of the arterial pressure and the loss of the arteriovenous pressure differential. Generalized circulatory stasis must have developed under these conditions and led to stagnant anoxia of the brain. Finally, electrocardiograms of humans taken at Wright Field and Toronto have shown that such long periods of asystole do occur in man. The conclusion seems inescapable that bradycardia resulting from the stimulation of the carotid sinus may be so severe that the circulation to the brain becomes inadequate to maintain consciousness.

The association of unconsciousness with periods of asystole has been reported by workers studying those with hypersensitive carotid sinuses and also in cases of Adams-Stokes syndrome. Pertinently, Weiss and Baker (12) state that cardiac arrest produced by stimulation of the hypersensitive carotid sinus will be followed by unconsciousness in from 8 to 10 seconds while Penfield (13) reports that in the Adams-Stokes syndrome, unconsciousness occurs following 10 seconds of asystole.

The electroencephalograms taken from the rabbits present additional evidence of the depression of the central nervous system that may occur during negative acceleration. It is interesting that Engle, Romano and McLin (14) while studying patients with vaso-depressor and carotid sinus syncope, also observed during the recovery phase low amplitude, regular waves similar to those noted in the rabbits following acceleration.

Finally, although the bradycardia induced by carotid sinus stimulation could, in itself, account both for the confusion reported by men and the depression of the central nervous system observed in the animal experiments, other factors, such as a carotid sinus reflex of the central type (12), leading to cerebral depression without accompanying cardiovascular symptoms, may prove to be of comparable significance.

SUMMARY

Six humans were studied in the upright seated posture during exposure to headward centrifugal forces up to 3 *g* in intensity. Electrocardiograms were taken and arterial and venous blood pressures recorded at head level. Dogs and rabbits were exposed to accelerations up to 7 *g* in intensity and 2 minutes in duration. Electrocardiograms and electroencephalograms and arterial and venous pressures were recorded. The electrocardiograms showed vagus block with marked bradycardia and periods of asystole. Electroencephalograms taken immediately after negative acceleration revealed abnormal waves suggestive of brain disturbances.

The arterio- venous pressure differentials in both men and animals pointed to a decreased brain perfusion pressure and it is concluded that cerebral symptoms occurring at levels of headward centrifugal force in the range of 3 to 5 *g* may be due to changes of reflex origin. These disturbances could result from the marked carotid sinus stimulation that accompanies the increase in blood pressure at head level.

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Effects of Tetra-ethyl-ammonium Chloride on Pain Thresholds in Man

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ACHESON AND MOE (1) demonstrated that TEA (tetra-ethyl-ammonium ion) exerts its main actions through blockade of autonomic ganglia. Brown *et al.* (2) have carefully studied the effects of intravenous TEA on humans, particularly with respect to vascular actions. Moe and his co-workers (3) have demonstrated a blocking effect of TEA on the action of acetylcholine, nicotine and lobeline on the carotid body. Sonnenschein, Janowitz and Grossman (4, 5) have obtained evidence for a peripheral action of TEA in blocking the cutaneous axon reflexes for sweating, pilomotion and 'itchy skin.'

The present study, preliminary results of which have been published (6), demonstrates yet another action of TEA, apparently unassociated with ganglionic blockade. The suggestion that TEA may have an analgesic action has recently been made by Hewer and Keele (7) who reported that, in two experiments, 75 mg. and 100 mg. of TEA bromide given intravenously brought about a slight relief of ischemic pain. As will be shown, TEA raises the pain threshold of the finger pad (superficial pain), lowers that of the nail bed ('sympathetic' pain) and leaves practically unaffected that of the tooth (deep pain)[2]. The implications of these findings lead to several interesting considerations regarding the mode of action of TEA, as well as the mechanisms underlying the types of pain under examination.

METHODS

Four normal males were subjects for the 9 experiments. The tests were performed with the subjects recumbent, in a constant-temperature room at 78° F. (25.5° C.). Pain thresholds were determined on the blackened nail bed and pad of the distal phalanx of the middle finger. The testing instrument utilized radiant

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[2] The qualities of pain elicited from the finger pad and tooth, respectively, resemble those qualities described by Lewis (8) as belonging to superficial and deep tissues. Moreover, preliminary studies in this laboratory have shown that 'C fiber' pain, as in delayed or nail-bed pain, travels over sympathetic pathways as evidenced by the elevation of this threshold by stellate ganglion block (6). For this reason, we have called the pain of the nail-bed 'sympathetic' pain.

heat (6, 9, 10). The stimulus, provided by an electric light of variable intensity, was projected onto the test area through a condensing lens as a beam 2 mm. in diameter. The intensity was controlled by a variable transformer, calibrated in watts. The duration of the stimulus was limited to 4 seconds by an automatic shutter. The end-point was chosen as the first appearance of pain just at the end of the 4-second exposure. Before each measurement, the hand to be tested was immersed for one minute in a large vessel of water at 40° C., then dried and tested immediately.

Thresholds of the tooth were determined by stimulation of the pulp, through a metal filling, with an induced, highly damped sinusoidal current, according to the method of Goetzl, Burrill and Ivy (11). The instrument, calibrated from 0 to 4.2 volts in steps of 0.2 volt, delivered impulses at approximately one per second. The intensities of current, measured to the closest 0.05 volt, for the production of two end-points were determined. These were the first perception of non-painful sensation (T-1), and the appearance of true pain, with the affective component (T-2).

At the start of each experiment two or more control readings were made for each threshold. Following this, 100 mg. (1 cc.) of tetra-ethyl-ammonium chloride (Etamon chloride, Parke, Davis and Company) was injected into the median cubital vein within 5 seconds; threshold readings were made between 30 seconds and 2 minutes after the injection. An additional 200 mg. of TEA was injected, 3 to 5 minutes later, and threshold readings repeated. Finally, another 200 mg. of TEA was injected, and threshold readings were taken for the next 25 to 30 minutes, at intervals of 3 to 10 minutes. No attempt was made to determine circulatory effects of the drug, such as changes in pulse and arterial pressure, but note was made of the appearance of such subjective effects as metallic taste, cold and tingling in the extremities, drowsiness and diplopia.

RESULTS

The most consistent response observed, which occurred in every case, was the elevation of threshold of the finger pad. An average maximum rise of 12 per cent was detected within 5 minutes after the last of the 500 mg. of TEA was injected. After 10 minutes, the effect gradually diminished, until at 30 minutes this threshold was elevated an average of only 6 per cent. The analgesic response proved to be statistically significant for the entire 5- to 30-minute period (table 1, fig. 1). The threshold of the nail bed, although showing an initial rise during the period of administration of TEA, later fell below the control value when the threshold of the pad was highest. Although small, this decrease in threshold is statistically significant (table 1), due to the relative consistency of the effect in each trial. No significant change occurred in either threshold of the tooth 10 minutes after TEA.

Figure 1 shows the relationship between pad and nail-bed thresholds

throughout the procedure. The statistical significance of the average readings at each point was plotted according to *t* values; for comparison, the mean percentage change of each threshold is represented. All points on the curve for the finger pad are within the 5 per cent (0.05) confidence limit, as is the low

TABLE 1. EFFECTS OF TEA ON PAIN THRESHOLDS

10 minutes after 500 mg. TEA

SUBJECT	DATE	TOOTH 1		TOOTH 2		NAIL		PAD	
		Control	TEA	Control	TEA	Control	TEA	Control	TEA
		volts		*volts*		*watts*		*watts*	
C. C. P.	2/28/48	0.55	0.55	2.65	2.80	85.0	85.0	110	125
C. C. P.	3/ 8/48	0.55	0.60	3.00	3.40	81.7	75.0	120	130
C. C. P.	5/ 8/48	0.63	0.55	3.00	3.20	60.0	55.0	102	110
C. C. P.	10/28/48	0.43	0.47	1.15	1.50	68.5	60.0	111	115
J. L.	5/ 1/48	0.50	0.60	1.15	1.10	62.5	60.0	82	100
J. L.	5/12/48	0.60	0.65	1.15	1.20	68.5	60.0	85	100
A. H.	10/28/48	0.30	0.30	1.70	1.65	72.5	70.0	105	120
R. R. S.	3/ 1/48	1.10	1.00	1.60	1.60	87.0	90.0	119	140
R. R. S.	10/28/48	0.42	0.40	1.20	1.10	68.5	65.0	120	125
Means		0.564	0.569	1.844	1.950	72.7	68.9	106	118.3
Mean differences		+0.005v.		+0.106v.		−3.8w.		+12.3w.	
Standard error		0.021v.		0.060v.		1.28w.		1.96w.	
P		0.8		0.1		0.02		0.001	

Tooth 1 and *tooth 2* refer respectively to perceptive and affective tooth thresholds. All TEA values are those obtained 10 minutes (8 to 12 min.) after injection of last 200 mg. TEA. *P* was calculated from the *t* values for mean differences.

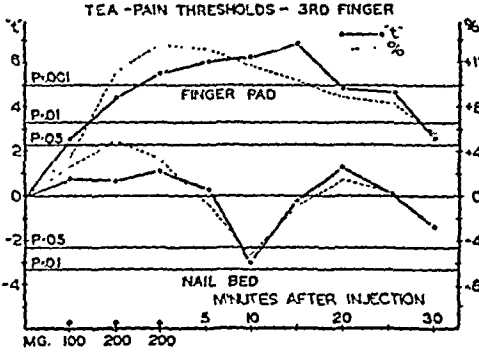

Fig. 1. PERCENTAGE VALUES are plotted for pain thresholds at the time of each measurement. The dotted lines represent the mean percentage changes of the 2 thresholds (nail and pad) for the 9 experiments. The solid lines represent the *t* values of the data at each test period. All points on the upper solid curve which lie above the horizontal line marked $P = 0.05$ are significant within the 5 per cent confidence limit. Similarly, those on the lower curve (nail bed) below $P = 0.05$ are significant within the 5 per cent limit.

point on the nail-bed curve. The rather close parallelism between the two curves for each threshold indicates a relatively constant variance of the readings throughout the experiment.

In contrast, figure 2, constructed in the same manner as figure 1, for T-1 and T-2, demonstrates the lack of significant effect on the tooth. Only at one point does T-2 become significant, while T-1 nowhere reaches the 5 per cent

limit, even though its percentage increase is marked towards the end of the curve.

The main side effects of the drug that have been noted by others (2) were observed in these experiments. Within 20 to 30 seconds of injection of each portion of the total dose, a transitory *metallic taste* was experienced, followed by a cold, tingling sensation in the hands and feet. When the hand was in a 40° C. bath, the sensation was that of sudden cooling of the water. Starting at about 2 to 3 minutes after the final injection, cycloplegia developed which lasted for 30 to 40 minutes. Much of the diplopia observed was due to a lack of suppression of near images while fixing on a distant object. (To our knowledge, the latter phenomenon has not been reported previously.) In two experiments, shortly after administration of the 500 mg. of TEA, a marked drowsiness developed, lasting 3 to 5 minutes, and associated with a ptosis that could not be completely overcome by voluntary effort. Of these various side effects, the

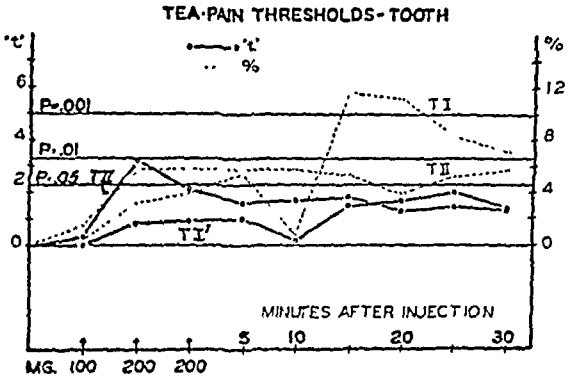

Fig. 2. MEAN PERCENTAGE CHANGES *and the t values of the changes in the 2 thresholds* are plotted in the same manner as fig. 1. T-1 is the first tooth threshold, and T-2 is the second.

only one which persisted as long as the elevation of the finger pad threshold was the cycloplegia, which in some cases lasted longer than the analgesia.

DISCUSSION

It appears from the data presented that TEA selectively raises the threshold for superficial pain in association with a fall in that of 'sympathetic' pain. Although the curve for the nail bed ('sympathetic' pain) is statistically significant at only one point (fig. 1), we believe that the reciprocal relationship of the responses between this threshold and that of the pad (*superficial pain*) is 'physiologically' significant and adds to our knowledge of the relationship between the thresholds of the finger nail bed and pad. On the other hand, although the curve for T-2 is statistically significant at one point (fig. 2), there is no reason to consider that the effect on either T-1 or T-2 is physiologically significant. The great percentage increase in T-1 towards the end of the experiment is indicative only of individual variation, as reflected by the low value of *P*.

Several explanations are possible for this selective analgesia, based on known actions of TEA. Blockade of the autonomic ganglia cannot explain this effect since preliminary experiments (6) indicate that procaine block of the stellate ganglion or the upper thoracic paravertebral ganglia raises the threshold of 'sympathetic' pain and not that of superficial pain. More likely, stellate block raises the threshold of 'sympathetic' pain through interruption of impulses along pathways passing through the ganglion, while the effect of TEA on superficial pain is not related to any ganglionic action.

The fact that drowsiness was noted after TEA in two experiments suggests a central depressant action as the basis for the analgesia, as in the case of general anesthetics. Chapman *et al.* (12) showed that 40 per cent nitrous oxide obtunds superficial pain, as tested by radiant heat; and Sonnenschein *et al.* (13), using tooth stimulation, demonstrated a significant rise in deep pain threshold with concentrations of nitrous oxide as low as 10 per cent or 20 per cent, associated with a general psychomotor depression. The fact, therefore, that TEA does not affect deep pain, even while producing drowsiness, mitigates against an action through general central depression. Moreover, the elevation of superficial pain threshold persisted for 25 to 30 minutes after the drowsiness had disappeared, whereas in the nitrous oxide experiments (13) pain threshold fell to normal within 5 to 10 minutes of the disappearance of drowsiness produced by 30 per cent or 40 per cent concentrations of the gas.

Evidence exists (4, 5) that TEA has certain peripheral actions, at least in the skin. The inhibition of the axon reflexes of sweating and pilomotion appears to be due to a 'nicotine-blocking' effect on the afferent arms of sympathetic axon branches, the latter behaving pharmacologically like ganglia. The mechanism of inhibition of the axon reflex responsible for 'itchy skin' is obscure. It is conceivable, then, that TEA may inhibit superficial pain by acting upon the peripheral receptor system in the skin, while not affecting the mechanisms responsible for deep and 'sympathetic' pain. This could be accomplished through competitive inhibition of some substance involved in mediation of superficial pain. Pending further investigation, this question must remain open.

An additional possibility is that TEA selectively blocks the nerve fibers responsible for superficial pain. Again, there are no reported findings to substantiate this hypothesis.

Finally, a central (cortical or subcortical) locus of action may be considered, not in the sense of a general depression, as discussed above, but rather from the point of view of interference with specific mechanisms concerned with mediation of pain. The potent analgesic drugs, heroine, dilaudid and L-methadone, manifest selective actions (6) on the three pain thresholds. Heroine (2 mg.), for example, causes a marked elevation (73 per cent) of deep pain (T-2) threshold, while showing only a peak effect of 10 per cent on superficial pain

threshold. Dilaudid raises superficial pain threshold 17 per cent but raises the deep pain (T-2) threshold 71 per cent and has no significant effect on 'sympathetic' pain. The L-methadone (5 mg.) affects all thresholds about equally (17-24 per cent). No satisfactory explanation exists for these observations, but since these drugs are believed to exert their analgesic action primarily on cortical or thalamic centers, it might be considered that the three types of pain are subserved by separate central mechanisms, and that each agent has characteristic selective effects on these various mechanisms. On the basis of the above hypothesis, TEA could theoretically have a highly localized action on the central mechanism responsible for superficial pain.

The apparently anomalous fall in 'sympathetic' pain threshold deserves consideration. It has been observed (6) that under certain other experimental conditions there is a reciprocal relationship between superficial and 'sympathetic' pain when measured on the same finger. When 'sympathetic' pain threshold is elevated by stellate or paravertebral ganglion block, the superficial pain threshold may decrease slightly. Conversely, when the superficial pain threshold of the third digit is raised by partial block of the median nerve with 0.5 per cent procaine, the 'sympathetic' pain threshold decreases. These results, along with those of TEA, suggest that the two pain systems are normally in balance and that inhibition of one may result in an over-action of the other. The basis of this relationship is obscure, but may be a process of cortical summation, balance in the internuncial pool, or a peripheral effect.

Thus, a number of possible explanations exist for the selective action of TEA in raising superficial pain threshold and lowering 'sympathetic' pain threshold. None of these, however, has a sufficiently firm experimental basis. Further investigations are in progress in this laboratory to elucidate the underlying mechanisms of the effects reported in this paper.

SUMMARY

Tetra-ethyl-ammonium chloride, administered intravenously, raises the threshold of superficial pain (finger pad), lowers that of 'sympathetic' pain (nail bed), and leaves relatively unaffected that of deep pain (tooth). Several explanations for this action are considered; in the present state of our knowledge, none of these is entirely satisfactory.

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A New Method of Measuring Fatigue by the Threshold Stimulus of the Achilles Tendon Reflex

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IT IS INCONTESTABLE that a strenuous study on the counterplan for the prevention of industrial fatigue is extremely important for increasing production, preventing accidents and diseases, and safeguarding working capacity. As a matter of fact, industrial fatigue is not an individual fatigue, but a group fatigue. It is obvious, therefore, that the method for its measurement should be accurate and so simple at the same time that the degree of fatigue of the working group can be measured in a short time. Only methods having such conditions permit the determination of group fatigue.

Wickwire *et al.* (1, 2) have reported that the threshold stimulus of the knee jerk may be used as a test for physical fitness. Trying Wickwire's experiments, we (3–5) have confirmed that the threshold stimulus for the knee jerk is raised after work, either physical or mental, and that it continues to rise as the work goes on. It is found, therefore, that the threshold of the knee jerk can be used as an index of both physical and mental fatigue. It is possible that, after work, the threshold stimulus of the Achilles tendon reflex is also raised at the same time as the knee jerk. If this is true, we may use the Achilles jerk for the measurement of physical and mental fatigue; with this end in view we have carried out the present experiments.

Although the Achilles tendon reflex is very often examined by the clinicians, nobody has ever undertaken its quantitative determination, and the relation of fatigue with the threshold stimulus for the Achilles jerk has never been reported in the literature.

METHODS

For the present experiments, 305 healthy men between the ages of 16 and 23 who showed no abnormality in either the knee or Achilles jerks were used. Of them 145 were Northern Chinese engaged in public works which lasted 10 hours in the daytime. The remaining 160 young men were Japanese telegraphers; 80 of them worked in the daytime and the rest in the nighttime. While the Chinese were physical workers, the work of the Japanese was exclusively mental, and lasted 8 hours every day either in the daytime or in the nighttime.

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In order to determine the threshold stimulus of the Achilles tendon reflex, we have devised a swinging hammer attached to a protractor, the position of which could be freely changed through rack and pinion (fig. 1). The strength of stimulus was increased or decreased by changing the falling angle of the hammer. At first the hammer is placed on the middle point of the Achilles tendon, its handle being adjusted to 0° of the protractor. The hammer is then raised to certain degrees and falls on the tendon to evoke reflex. Jendrassik's maneuver should be performed with a view to deviating the attention of the subject under examination.

The hammer used may be regarded as a simple pendulum moving in a vertical plane (its head weighed 33 gm.; its handle weighed 3 gm. and was 20 cm. long).

Let θ = falling angle of the hammer; l = length of the handle of the hammer (20 cm.); h = vertical falling distance of the hammer; m = weight of the hammer (33 gm.); g = acceleration of gravity; $P.E.$ = potential energy of hammer = mgh; $K.E.$ = kinetic energy of hammer = $1/2\ mv^2$; M = momentum = mv; f = average force on tendon; t = time necessary for the hammer to come to a standstill after it has struck tendon; F = strength of stimulus required for eliciting reflex.

$h = l \sin\theta \qquad P.E. = mgl. \sin\theta$

On the tendon, $P.E. = 0 = K.E.$ $mgl. \sin\theta = 1/2\ mv^2$ or $v = \sqrt{2\ gl}\sqrt{\sin\theta}$

$M = mv = ft.$ or $f = mv/t = m\sqrt{2\ gl}\sqrt{\sin\theta}/t$

Because t is small, the total force is applied before the tendon has a chance to move. Therefore the strength of stimulus (F) may be indicated by $F = mv = m\sqrt{2\ gl}\sqrt{\sin\theta}$.

Therefore the strength of stimulus is a *positive function of* 0 *up to* $\theta = 90°$.

Since Griesbach (6) reported that the double point threshold is augmented by exhaustion, many authors have been utilizing this test for the study of fatigue. We measured, therefore, the double point threshold on the malar arch with Sieveking's esthesiometer at the same time as the threshold stimulus of the Achilles tendon reflex for comparison purpose, each threshold having been determined before and after work. In order to know the successive change of these two thresholds in the course of physical and mental work and to find if there exists a relation between the threshold stimulus for the Achilles tendon reflex and that for the knee jerk, we have measured every two hours these three thresholds of 20 subjects from among the physical workers and the mental daytime workers, respectively. The method of measuring the threshold stimulus for the knee jerk has already been described in our previous papers (3, 4).

RESULTS

The average θ values for each group of workers are summarized in tables 1 and 2 from which it is seen that both the threshold stimulus of the Achilles

tendon reflex and the double point threshold are increased after work, either physical or mental.

In order to verify that the difference of threshold before and after work, namely the increase of threshold after work, exists with certainty, the probable error of the difference ought to be less than one third of the difference itself. Now, let us compute the average value of threshold difference d and its probable error PEd from the difference of each subject before and after work, then we obtain the value of d/PEd which is shown in table 3. It is obvious from table 3 that the threshold stimulus for the Achilles tendon reflex is infallibly raised after all kinds of work, whereas the increase of double point threshold is certain only after physical work and uncertain after mental work.

Fig. 1. HAMMERING DEVICE for the measurement of threshold stimulus of Achilles tendon reflex

With regard to the successive change of the threshold for the knee and Achilles jerks and that of the double point threshold, the results in the average values obtained in the course of daytime work are shown in figures 2 to 4.

It is noteworthy that, regardless of the kind of work, the threshold stimulus of the Achilles tendon reflex gradually increases, as the working hour goes by, and that its rate of increase nearly coincides with that of the knee jerk reflex so that the two curves showing the change of threshold stimuli run almost parallel with each other. As regards the double point threshold, the curve of its successive change in the course of physical work is very irregular and does not rise in accordance with the progress of work. The results with reference to the successive change of the double point threshold in the course of mental work have been omitted for the reason that its increase after work is theoretically uncertain.

DISCUSSION

It is evident that the degree of fatigue increases in accordance with the progress of work, either physical or mental. From the fact that the threshold stimulus for the Achilles tendon reflex not only increases after any kind of work,

but gradually rises as the working hour goes by, it would seem that the threshold stimulus for the Achilles tendon reflex may be used for the measurement of fatigue, particularly for the study of industrial fatigue, since our method of measuring threshold is both accurate and simple. It is of significance that the two curves showing the change of threshold run nearly parallel with each other.

It is obvious that the double point threshold cannot be used as a test for mental fatigue for the reason already stated, and owing to its irregular change, it cannot be regarded as a suitable index to physical fatigue.

TABLE 1. THRESHOLD STIMULUS OF ACHILLES TENDON REFLEX AND DOUBLE POINT THRESHOLD BEFORE AND AFTER PHYSICAL WORK

(The data given are the average values for each group.)

	THRESHOLD OF ACHILLES TENDON REFLEX	DOUBLE POINT THRESHOLD
	θ and P.E.	*mm. and P.E.*
Before work	14.64 ± 0.236	18.19 ± 0.199
After work	26.19 ± 0.503	23.52 ± 0.185
Difference	11.55	5.33

TABLE 2. THRESHOLD STIMULUS OF ACHILLES TENDON REFLEX AND DOUBLE POINT THRESHOLD BEFORE AND AFTER MENTAL WORK

(The data given are the average values for each group.)

		THRESHOLD OF ACHILLES TENDON REFLEX	DOUBLE POINT THRESHOLD
		θ and P.E.	*mm. and P.E.*
Daytime work	Before work	21.25 ± 0.766	16.29 ± 0.361
	After work	32.50 ± 1.055	16.46 ± 0.361
	Difference	11.25	0.17
Nighttime work	Before work	24.38 ± 0.696	14.60 ± 0.380
	After work	37.13 ± 0.984	15.57 ± 0.419
	Difference	12.75	0.97

From the results obtained in the mental workers, it is seen that there is more increase of threshold stimulus after nighttime work than after daytime work (see table 2), which means that the degree of fatigue is greater in the nighttime workers than in the daytime workers. Comparing the threshold stimulus before work of the daytime workers with that of the nighttime workers, the latter shows higher value than the former. It appears from this that the nighttime workers were already in a state of slight fatigue before starting to work. The reason is apparently due to the fact that, while the daytime workers could start working in the morning after a night's sleep, the nighttime workers had to begin their work in the evening after a whole day's rest which could not completely heal the fatigue of the previous night. As the efficiency of workers

is in inverse proportion to the degree of fatigue, it is necessary, therefore, to take measures to enable them to sleep as soundly in the daytime as in the nighttime. By the determination of the threshold for the Achilles tendon reflex before work, it is possible to know whether or not the fatigue of the preceding night has been entirely relieved.

TABLE 3. VALUE OF D/PED

	THRESHOLD OF ACHILLES TENDON REFLEX	DOUBLE POINT THRESHOLD
Physical work (daytime)	31.4 (significant)	26.6 (significant)
Mental work (daytime)	19.0 (significant)	0.4(insignificant)
Mental work (nighttime)	15.7 (significant)	2.8 (insignificant)

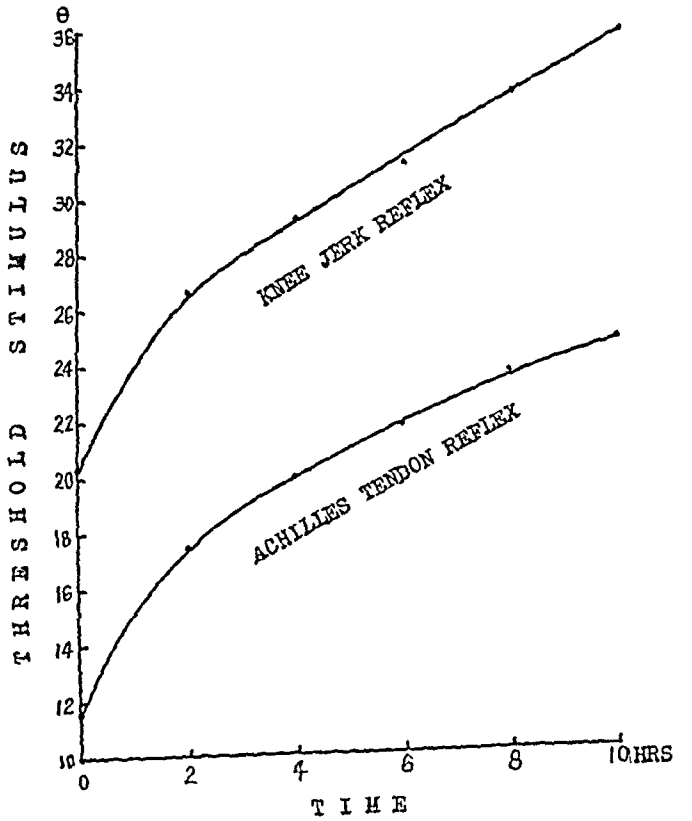

Fig. 2. SUCCESSIVE CHANGE of threshold stimulus in the course of physical work

It is noteworthy that the threshold stimulus before work of the physical workers is much lower than that of the mental workers (see tables 1 and 2). In reality, we were surprised during the present experiments at the unexpectedly great difference in threshold between the two groups of workers, one being Chinese and the other Japanese. It is not well known why there exists such marked difference in threshold at rest between the two races. It has been reported (7) that the normal threshold stimulus for the knee jerk is lowered as

a result of the administration of vitamin B_1. In the present experiments, the physical workers were Northern Chinese whose staple food consists of cereals

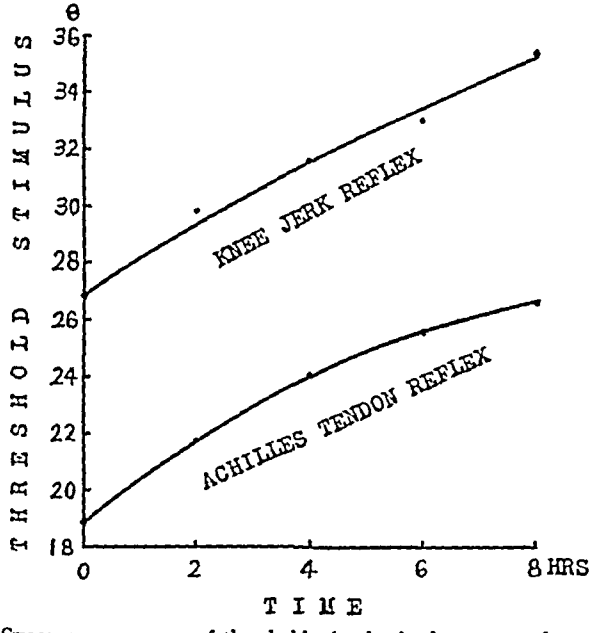

Fig. 3. SUCCESSIVE CHANGE of threshold stimulus in the course of mental work

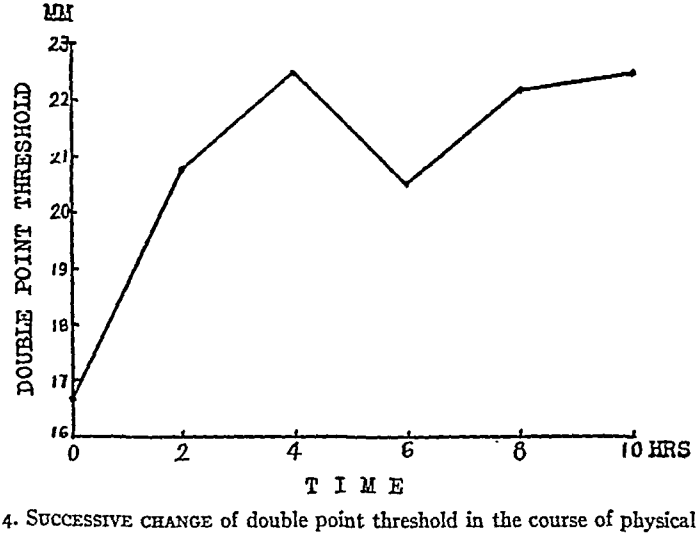

Fig. 4. SUCCESSIVE CHANGE of double point threshold in the course of physical work

which are rich in vitamin B, while the mental workers were Japanese eating principally polished rice. It has been pointed out (8, 9) that, contrary to Japan, beriberi is not known in North China where polished rice does not serve as

staple food. The difference in the normal threshold stimulus of the Achilles tendon reflex between the two groups of workers is, therefore, presumably due to the different supply of vitamin B_1.

SUMMARY

Using a special hammering device, experiments on 305 workers have been carried out in order to determine whether or not the threshold stimulus for the Achilles tendon reflex could be used as a test for both physical and mental fatigue, the threshold stimulus for the knee jerk and the double point threshold having been measured at the same time for comparison.

The threshold stimulus for the Achilles tendon reflex is raised after either physical or mental work both in the daytime and in the nighttime. As the working hour goes by, the threshold stimulus for the Achilles tendon reflex increases in parallel with the threshold stimulus for the knee jerk. Accordingly, the threshold stimulus of the Achilles tendon reflex may be used as a test for measuring physical and mental fatigues. It seems to be particularly suited for the study of group fatigue, such as industrial fatigue, for the reason that the procedure of the threshold measurement is accurate and rather simple by the author's method. Although the double point threshold increases with certainty only after physical work, it cannot be used as a test for physical fatigue, as it does not increase in parallel with the progress of work, showing even irregular fluctuation in the course of the working hour.

Measures should be taken to enable night workers to sleep as soundly in the daytime as in the nighttime, so that their fatigue of the previous night may be completely healed by the sound sleep of a whole day. The determination of the threshold for the Achilles tendon reflex before work makes it possible to know whether or not the fatigue of the preceding night has been entirely relieved.

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Relationship Between Body Build and Capacity for Exercise

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DURING THE COURSE of a routine assessment of the physical fitness of some 7000 Ceylonese subjects (1), data on the relationship between body build and capacity for various types of exercise have been collected. Male and female subjects from the age of 10 years upwards performed the following tests: *a*) The Harvard Step Test (2), from which the fitness index pulse and the fitness index blood pressure (3) were calculated; *b*) the Endurance Step Test (3), which consists of stepping on a 20-inch step at a rate of 45 step-up and step-down cycles per minute for as long as possible, from which the endurance time (3) of each subject was obtained; *c*) the Exhaustion Step Test (4), which consists of stepping on a 20-inch step at a rate of 30 cycles per minute for as long as possible and from which the exhaustion time was obtained; *d*) a Strength Test (5), which consisted of lifting a series of graded weights a height of 20 inches from the floor; and *e*) a Speed Test (4), which consisted of running 100 yards as fast as possible.

In addition for each subject the following measurements were made: height, weight, surface area (Du Bois), chest circumference (rest), chest circumference (inspiration), chest breadth, chest depth, chest length, bi-acromial diameter, bi-iliac diameter, leg length and bi-zygomatic diameter. From these measurements the following indices have been calculated: weight/height, leg length/height, bi-acromial/height, bi-iliac/height, chest circumference/height, bi-iliac/bi-acromial, chest depth/chest breadth, chest length/sitting height, chest breadth/sitting height.

RESULTS

The coefficients of correlation between the fitness indices obtained from the 5 fitness tests and the anthropometric characters have been calculated for various groups of subjects. The fitness indices vary significantly with age and sex (4) so that generally we have considered each sex and each age or age group separately. Except when stated otherwise, the following figures refer to males of the age group 21 to 25 years; similar results were obtained for females and at other ages.

Fitness Index Pulse (*Harvard Step Test*). For our groups of subjects the fitness index pulse is correlated significantly with bi-iliac diameter/height,

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chest circumference/height, the bi-iliac diameter and the bi-zygomatic diameter, but is not correlated with any of the other anthropometric characters (table 1).

TABLE 1. CORRELATION BETWEEN FITNESS INDICES AND ANTHROPOMETRIC CHARACTERS (MALE CEYLONESE SUBJECTS AGED 21 TO 25 YEARS, NUMBER OF SUBJECTS IN GROUP, 406)

FITNESS INDEX	ANTHROPOMETRIC CHARACTER	COEF. OF CORREL.	SIGNIF. OF CORREL., P	FITNESS INDEX	ANTHROPOMETRIC CHARACTER	COEF. OF CORREL.	SIGNIF OF CORREL., P
Fitness index pulse	bi-iliac/ht.	+0.3014	0.01	Resting systolic blood pressure	bi-iliac/ht.	−0.2438	0.02
	chest circum/ht.	+0.2737	<0.02		chest l./sitting ht.	−0.2992	0.01
	bi-iliac diam.	+0.2432	<0.05		weight	+0.21327	0.05
	bi-zygomatic diam.	+0.2079	0.05		height	+0.2842	0.01
Fitness index blood pressure	wt/ht.	−0.3201	0.01	Strength	surface area	0.6100	<0.001
	chest depth/chest breadth	+0.3114	0.01		chest circum/ht.	0.2384	0.02
	chest breadth	−0.2492	0.02		chest circum.	0.2952	0.01
	chest length	−0.2120	0.05		chest breadth	0.2554	0.02
	weight	−0.3438	<0.01		leg length	0.2778	0.01
	height	−0.2762	0.01		bi-iliac diam.	0.3705	0.001
Endurance time	bi-iliac diam.	−0.2451	0.02		bi-acromial diam.	0.2435	0.02
	bi-iliac/bi-acromial	−0.2114	0.05		bi-zygomatic diam.	0.3155	0.01
					weight	0.2857	0.01
ting pulse rate	chest circum/ht.	−0.2488	0.02				
	chest l./sitting ht.	+0.2848	0.01				
	chest length	−0.2552	0.02				
	bi-iliac diam.	−0.2219	0.05				
	weight	−0.2409	0.02				

Exhaustion time and speed gave similar, but slightly more significant, correlations to those given for strength. Similar correlations were found for subjects of both sexes and at all ages between 10 and 40 years inclusive.

We have already shown that the fitness index pulse is correlated in a negative fashion with the resting pulse rate (6), and we have also found that the chest circumference/height and the bi-iliac diameter, among other characters, are significantly but negatively correlated with the resting pulse rate (table 1). Do these two characters influence the fitness index pulse because they influence the resting pulse rate?

If we calculate the coefficient of partial correlation between chest circumference/height and fitness index pulse, keeping pulse rate constant, we get a value of +0.2011 (P = 0.05), which is just significant. Calculation of the partial correlation coefficient between bi-iliac diameter and the fitness index pulse, keeping pulse rate constant, gives a value of +0.1742, which is not significant.

Fitness Index Blood Pressure (*Harvard Step Test*). This index is significantly and negatively correlated with weight/height, chest breadth, chest length, weight and height, and there is a positive correlation with surface area and chest depth/chest breadth (table 1). The fitness index blood pressure is also negatively correlated with the resting systolic blood pressure (6) which in turn is positively correlated (table 1) with weight and height in our groups of subjects. The partial correlation coefficient, keeping the resting systolic blood constant, between fitness index blood pressure and weight is −0.2804 (P = 0.01), and that between fitness index blood pressure and height is −0.1081 (P = >0.05). Therefore, the influence of height upon the fitness index blood pressure is due solely to its influence upon the resting systolic blood pressure.

Endurance Time (*Endurance Step Test*). Endurance time is correlated in a negative way with the bi-iliac diameter and the bi-iliac/bi-acromial index (table 1). That is to say, that those subjects with narrower hips performed severe exercise, involving the assumption of a rapidly increasing oxygen debt, for a longer time than did those subjects with broader hips.

Strength is positively and significantly correlated with surface area, chest circumference/height, chest circumference, chest breadth, leg length, bi-iliac diameter, bi-acromial diameter, bi-zygomatic diameter and weight. That is to say that the stronger subjects were those with the broader hips, the broader shoulders, the broader chests, the broader faces and the bigger weights and surface areas.

Exhaustion Time (*Exhaustion Step Test*). This shows similar and positive correlations to strength with, in addition, a significant correlation with height (coefficient of correlation = +0.2742; P = 0.01).

Speed gave exactly similar correlations to those given by exhaustion time.

SIGNIFICANCE OF RESULTS

Racial Differences. Our data indicate that exercise performance ability is correlated with certain anthropometric characters. The existence of differences between anthropometric measurements and indices for subjects of different racial extraction is well established; we should expect, therefore, to find racial differences in exercise ability. That such differences can be detected has already been indicated by us (5), and our present data throw further light on this problem. To take our age group 21 to 25 years as an example, the following

mean fitness indices for the different racial groups of subjects are obtained (table 2).

The fitness index pulse does not vary significantly between the racial groups, but yet there are significant differences between the races when we consider the anthropometric characters, bi-iliac/height, chest circumference/height and bi-zygomatic diameter (7), which characters are related to the fitness index pulse. There are other factors which can influence the fitness index pulse. Thus we have shown that it is correlated negatively with the resting pulse rate (6), and with leg muscle development (4).

Neither resting pulse rate nor leg muscle development vary significantly with race (8, 9) which is in conformity with the absence of significant differences between the mean fitness indices for the racial groups.

Significant racial differences are to be found in the case of the fitness indices, fitness index blood pressure, endurance time, strength, exhaustion time and speed, and these differences will be seen to parallel to a good degree the relevant racial differences noted between the anthropometric characters, if we remember that endurance time is negatively correlated with bi-iliac/bi-acromial and with bi-iliac diameter and that fitness index blood pressure shows both positive and negative correlations (table 3).

Therefore, where racial differences in fitness indices are evident, these are mirrored by similar differenees in the co-related anthropometric characters.

Environmental Differences. The fitness of subjects also varies with their gross environment (5). Thus, Ceylon can be sharply divided into the City of Colombo, the wet zone and the dry zone. This division is made chiefly on the basis of the average rainfall during the S.W. Monsoon and it is a distinct division from the points of view of the fertility of the soil, the prosperity, the nutrition and the health of the people. The differences between the mean fitness indices of the groups of subjects (Sinhalese, aged 21 to 25 years) living in these three distinct environments are shown in table 4.

These groups of people also show significant differences between their mean anthropometric characters and it is evident from a study of table 3 that there is a very close correlation between these anthropological differences and the differences noted to exist between their fitness indices. This is true for all the fitness indices and the body measurement differences would seem to form a reasonable basis for the explanation of the differences between the fitness of the peoples of the three environments.

Economic Status. We have also classified our subjects according to their economic status. This classification is based upon family income records, and the occupations, ages and number of people in the family. The following three economic levels have been distinguished: *a*) *Low Income Group*, with a family income of less than 20 rupees per month per adult consumption unit; *b*) *Intermediate Income Group*, with a family income of between 20 and 50 rupees per

TABLE 2. INFLUENCE OF RACE UPON FITNESS OF CEYLONESE MALES, AGED 21 TO 25 YEARS

FITNESS INDEX	RACE	NO. OF SUBJECTS	MEAN INDEX	S. E. OF MEAN, ±	SIGNIF. OF DIFF. BETWEEN MEANS	FITNESS INDEX	RACE	NO. OF SUBJECTS	MEAN INDEX	S. E. OF MEAN, ±	SIGNIF. OF DIFF. BETWEEN MEANS
Fitness index pulse	Sinhalese	273	84.6	0.98	none significant	Strength	Sinhalese	226	84.3	1.00	
	Ceylon Tamil	67	82.6	2.97			Ceylon Tamil	52	71.7	1.85	< Sinhalese. P < 0.001
	Indian Tamil	34	87.4	1.81			Indian Tamil	23	70.2	1.72	< Sinhalese. P < 0.001
	Ceylon Moor	23	75.8	5.93			Ceylon Moor	23	68.4	2.67	< Sinhalese. P < 0.001
Fitness index blood pressure	Sinhalese	274	77.8	1.07	< Indian Tamil. P = 0.02	Exhaustion time	Sinhalese	220	78.5	38.7	
	Ceylon Tamil	67	76.6	1.57	< Indian Tamil. P = 0.01		Ceylon Tamil	52	64.2	49.2	< Sinhalese. P = 0.02
	Indian Tamil	34	82.5	1.41			Indian Tamil	22	49.1	81.3	< Sinhalsee. P = 0.001
	Ceylon Moor	23	67.4	7.21			Ceylon Moor	21	48.9	83.2	< Sinhalese. P = 0.001
Endurance time	Sinhalese	278	80.8	2.17	> Ceylon Tamil. P = 0.01	Speed	Sinhalese	220	11.71	0.436	
	Ceylon Tamil	62	63.0	6.13			Ceylon Tamil	52	13.25	0.490	< Sinhalese. P = 0.05
	Indian Tamil	33	79.0	5.07	> Ceylon Tamil. P = 0.05		Indian Tamil	22	16.24	0.507	< Sinhalese & Ceylon Tamil P < 0.001
	Ceylon Moor	23	74.9	5.77			Ceylon Moor	21	16.44	0.541	

Values are mean ± standard error of the mean. P = probability. Strength is measured in kg. weight lifted. The time indices are given in seconds. Speed is measured by the time to run 100 yards.

TABLE 3

FITNESS INDEX	RELATED ANTHROPOMETRIC CHARACTER	SIGNIFICANT RACIAL DIFFERENCES	SIGNIFICANT ENVIRONMENTAL DIFFERENCES	SIGNIFICANT ECONOMIC DIFFERENCES	FITNESS INDEX	RELATED ANTHROPOMETRIC CHARACTER	SIGNIFICANT RACIAL DIFFERENCES	SIGNIFICANT ENVIRONMENTAL DIFFERENCES	SIGNIFICANT ECONOMIC DIFFERENCES
Fitness index, pulse		none	wet zone > Colombo & dry zone	intermed. > low & high	Strength, exhaustion, time and speed	bi-acromial	Sinhalese, Ceylon Tamil & Ceylon Moor > Intermed.	wet zone > dry zone & Colombo	intermed. & higher > low
	bi-iliac/ht.	Indian Tamil > Ceylon Tamil	none	intermed. > low		weight	Sinhalese, Ceylon Tamil, & Ceylon Moor > Indian Tamil	wet zone > dry zone & Colombo	higher intermed. > low
	chest circum/ht.	Sinhalese > Ceylon Tamil & Indian Tamil	wet zone > Colombo & dry zone	none		chest circum.	Sinhalese, Ceylon Tamil & Ceylon Moore > Indian Tamil	wet zone > dry zone > Colombo	higher & intermed. > low
	bi-iliac	none	wet zone > Colombo & dry zone	intermed. & higher > low		chest breadth	Sinhalese, Ceylon Tamil > Indian Tamil	wet zone > dry zone > Colombo	higher > intermed. > low
	bi-zygomatic	Sinhalese & Ceylon Moor > Indian Tamil	dry zone > Colombo	intermed. > higher & low		chest length	Sinhalese > Ceylon Tamil	wet zone > dry zone	higher & intermed. > low

Endurance time		Sinhalese > Ceylon Tamil Indian Tamil > Ceylon Tamil	Colombo > dry zone > Colombo	intermed. > low & higher	Blood pressure		Indian Tamil > Sinhalese & Ceylon Tamil	dry > wet	low > higher
	bi-iliac/bi-acromial	Ceylon Tamil > Sinhalese Indian Tamil > Sinhalese & Ceylon Moor	Colombo & dry zone > wet zone	low > intermed. & higher		weight/ht.	Indian Tamil > Ceylon Tamil, Sinhalese & Ceylon Moor	dry & Colombo > wet	lower > intermed. > higher
	bi-iliac	none	wet zone > dry zone & Colombo	intermed. & higher > low		chest length/ chest breadth	none	dry & Colombo > wet	low > intermed. & higher
Strength, exhaustion, time & speed		Sinhalese > Ceylon Tamil & Ceylon Moor	wet zone > dry zone > Colombo	higher > intermed. > low		chest breadth	Indian Tamil > Ceylon Tamil & Sinhalese	Colombo dry > wet	low > intermed. > higher
	surface area	Ceylon Tamil > Sinhalese > Indian Tamil. Ceylon Moor > Sinhalese & Indian Tamil	wet zone > dry zone & Colombo	higher > intermed. > low		chest length	Sinhalese > Ceylon Tamil	dry > wet	low > intermed. & higher

TABLE 3—*Concluded*

FITNESS INDEX	RELATED ANTHROPOMETRIC CHARACTER	SIGNIFICANT RACIAL DIFFERENCES	SIGNIFICANT ENVIRONMENTAL DIFFERENCES	SIGNIFICANT ECONOMIC DIFFERENCES	FITNESS INDEX	RELATED ANTHROPOMETRIC CHARACTER	SIGNIFICANT RACIAL DIFFERENCES	SIGNIFICANT EVIRONMENTAL DIFFERENCES	SIGNIFICANT ECONOMIC DIFFERENCES
	bi-iliac	none	wet zone > Colombo & dry zone	higher & intermed. > low		weight	Indian Tamil <Sinhalese, Ceylon Tamil & Ceylon Moor	Colombo < dry < wet	low < intermed. < higher
	bi-zygomatic	Sinhalese & Ceylon Moor > Indian Tamil	dry zone > wet zone	intermed. > higher & low		height	Indian Tamil Sinhalese & Ceylon Tamil	Colombo < dry < wet	low < intermed. < higher
	chest circum./ht.	Sinhalese > Ceylon Tamil & Indian Tamil	dry zone > Colombo & wet zone	none					
	leg length	Sinhalese > Indian Tamil Ceylon Tamil > Indian Tamil	wet zone > Colombo & dry zone	intermed. & higher > low					

month per adult consumption unit; and *c*) *Higher Income Group*, with a family income of more than 50 rupees per month per adult consumption unit. The differences between the mean fitness indices of subjects from these economic groups are detailed in table 3 along with the corresponding, relevant differences in the anthropometric characters. Again a good agreement between anthropometric differences and fitness differences is to be noted.

TABLE 4. INFLUENCE OF ENVIRONMENT UPON FITNESS OF CEYLONESE MALES AGED 21 TO 25 YEARS

FITNESS INDEX	ENVIRONMENT	NO. OF SUBJECTS	MEAN INDEX	S.E. OF MEAN, ±	SIGNIFICANCE OF DIFFERENCE BETWEEN MEANS
Fitness index pulse	wet zone	62	88.8	1.17	
	dry zone	127	82.7	1.39	< wet, P = 0.001
	Colombo	151	84.1	1.40	< wet, P = 0.01
Fitness index blood pressure	wet zone	57	76.0	1.94	
	dry zone	112	80.4	0.42	> wet, P = 0.05
	Colombo	145	76.6	3.29	
Endurance time	wet zone	62	66.2	5.09	< dry, P = 0.02
	dry zone	123	79.5	4.07	< Colombo, P = 0.05
	Colombo	126	88.6	2.83	> wet, P = 0.001
Strength	wet zone	38	95.5	1.84	> dry, P = 0.01
					> Colombo, P < 0.001
	dry zone	91	88.9	1.56	> Colombo, P <0.001
	Colombo	97	78.1	1.32	
Exhaustion time	wet zone	60	96.2	53.6	> P < 0.01
					> Colombo, P = 0.001
	dry zone	125	74.0	49.6	> Colombo, P = 0.001
	Colombo	130	51.7	47.5	
Speed	wet zone	60	11.10	0.492	> Colombo, P = 0.001
	dry zone	125	12.37	0.451	
	Colombo	130	13.63	0.448	

Values are mean ± standard error of the mean. *P* = probability. Strength is measured in kg. weight lifted. The time indices are given in seconds. Speed is measured by the time to run 100 yards.

The reality of the racial and environmental differences in fitness is well illustrated by an analysis of the variance of our results. Two typical analyses are given in APPENDIX A.

DISCUSSION

The relationship between exercise ability and body configuration has been remarked by many observers (2, 4, 7, 10). Thus, in agreement with our own findings, Seltzer (7) found that the people with the narrower hips were less efficient than others in performing moderate effort but were more efficient in

performing severe effort. The relationship which we have identified between the various fitness indices and the anthropometric characters do help to explain, in part, differences between the mean fitness indices of subjects of various racial, environmental or economic groups. The relationship between anthropometric differences and fitness indices differences is, however, not perfect. This is probably because other factors are involved in determining exercise ability. Thus, in all, for our own group of 7000 subjects we have found (6, 11, 12) significant correlations between:

a) *Fitness Index Pulse* and bi-iliac/height, chest circumference/height, bi-iliac diameter, bi-zygomatic diameter (positive correlation), leg muscle development, resting pulse rate and resting diastolic blood pressure (negative correlation);

b) *Fitness Index Blood Pressure* and chest length/chest breadth (positive correlation), weight/height, chest breadth, chest length, weight, height, resting systolic blood pressure, and resting diastolic blood pressure (negative correlation);

c) *Endurance Time* and vital capacity (positive correlation) bi-iliac diameter, bi-iliac/bi-acromial, and leg muscle development (negative correlation);

d) *Strength* and surface area, bi-iliac diameter, bi-zygomatic diameter, chest circumference/height, leg length, bi-acromial diameter, weight, chest circumference, chest breadth, resting systolic blood pressure, arm muscle development and resting blood hemoglobin level (positive correlation);

e) *Exhaustion Time* and similar factors to these enumerated for strength except that height is also positively correlated and there is no evidence of correlation with muscular development;

f) *Speed* has the same factors as for exhaustion time, but is correlated with leg muscle development.

We see, therefore, that strength, exhaustion time (which measures the ability to perform moderate muscular effort for a prolonged period) and speed of movement are very similarly related with body measurements, resting systolic blood pressure, muscular development and blood hemoglobin level. They are in fact correlated, in general, with those physical and physiological characteristics which increase with age during growth and they, themselves, also increase with age. Significant correlations are, however, obtainable even when the influence of age is eliminated as can be shown by calculating the partial correlation coefficients, keeping age constant, or by the data in table 5 where the mean characteristics possessed by Ceylonese subjects, of the same age (21 years) and grouped according to their strength, are given as an example.

The increase of strength, exhaustion time and speed with age may, therefore, be due to the increase of the co-related physical and physiological characters. Thus, for our group of 7000 subjects, weight, height, surface area, bi-iliac

diameter, bi-zygometric diameter, bi-acromial diameter, leg length, chest circumference, chest breadth, chest length, chest circumference/height (13), arm (but not leg) muscle development (9), the systolic blood pressure at rest (8) and the hemoglobin content all increase with age to reach maxima in early adult life. Most of these characters, too, are greater in Ceylonese males than in Ceylonese Females, and the males tend to have the greater strength, the greater exhaustion time and the greater speed.

Not all of these factors are, of course, equally important and many of them are inter-related with each other (e.g. systolic blood pressure with surface area, weight etc.) so that this relationship with fitness may be indirect,

TABLE 5. MEAN CHARACTERISTICS OF CEYLONESE SUBJECTS (AGED 21 YEARS) GROUPED ACCORDING TO STRENGTH

PHYSICAL OR PHYSIOLOGICAL CHARACTER	STRENGTH GROUP		
	>81.5 kg. (n = 60)	57.3 to 81.5 kg. (n = 155)	<57.3 kg. (n = 90)
Surface area	1.680 ± .00012	1.574 ± .00012	1.529 ± .00013
Bi-iliac diam.	26.6 ± 0.357	25.3 ± 0.303	24.3 ± 0.379
Bi-zygomatic diam.	12.75 ± 0.178	12.20 ± 0.173	11.86 ± 0.126
Bi-acromial diam.	37.06 ± 0.487	34.86 ± 0.476	33.88 ± 0.448
Weight	60.1 ± 0.83	56.6 ± 0.76	49.5 ± 0.81
Height	168.6 ± 1.80	162.3 ± 1.32	160.4 ± 1.45
Chest circum. (rest)	84.6 ± 0.46	81.4 ± 0.88	79.1 ± 0.59
Chest circum (inspir.)	89.3 ± 0.79	85.9 ± 0.74	83.8 ± 0.60
Chest circum. (ht.)	0.525 ± 3.8x 10^{-5}	0.506 ± 1.5x 10^{-4}	0.500 ± 1.3x 10^{-4}
Chest breadth	26.75 ± 0.575	24.7 ± 0.363	24.8 ± 0.421
Leg length	106.5 ± 0.75	103.7 ± 0.41	101.4 ± 0.42
Arm muscle develop.	30.2 ± 0.31	28.8 ± 0.26	27.6 ± 0.28
Systolic blood pressure	114.6 ± 3.02	104.5 ± 1.53	101.9 ± 2.31

Values are mean ± standard error of the mean. Surface area is measured in m^2. Weight is measured in kg; other measurements in cm.

but they do illustrate the type of subject who has the better performances at different exercise tasks and they agree, in general, with the findings of Woods, Brouha and Seltzer (10) and others, using somatotype ratings.

Fitness index pulse, fitness index blood pressure and endurance time are all indices which decrease with age and are correlated negatively with leg muscle development (4). The pulse and blood pressure indices are also correlated negatively with resting pulse rate and with resting blood pressure (6). Why do these indices decrease with age?

Leg muscle development is not influenced by age (9) but the resting systolic blood pressure increases with age to reach a maximum in early manhood and this rising blood pressure would favor a fall in the fitness indices. On the

other hand, the fitness index pulse is correlated negatively with the resting pulse rate and the resting pulse rate decreases with age, which decrease would favor a rise in the fitness index pulse. Again, the endurance time is correlated positively with the vital capacity (11) but the latter also increases with age to reach a maximum in adult life. The anthropometric characters also tend to increase or to remain constant with age so that, on the basis of the resting physical or physiological characters alone, we cannot account for the decrease with age of the fitness index pulse, the fitness index blood pressure and the endurance time.

Thus other factors than the purely physical characteristics of the body may be important. The hemoglobin content of the blood, for example, is greater in Ceylonese males than in Ceylonese females, is greater in subjects of the wet zone than in those living in the dry zone, is greater in subjects from the higher income group and is greater in Sinhalese subjects than in Ceylon Tamil, Ceylon Moor or Indian Tamil subjects (14). Strength, exhaustion time and speed, we have seen, have a similar variation.

Arm muscle development, like strength, is greater in adult Sinhalese than in Ceylon Tamils and Indian Tamils, but the Ceylon Moor adult male has better developed arm muscles relative to height than has the Sinhalese man (9) and yet the Sinhalese are the stronger. Leg muscle development does not vary between the Ceylonese races, but it does vary with environment. Thus, male subjects, aged 21 to 25 years and living in Colombo, have better developed leg muscles than have male subjects living in the dry zone (9) and, although endurance time is correlated negatively with leg muscle development, the Colombo subjects have a greater mean endurance time than have the dry zone subjects. Therefore, variations in muscular development alone cannot explain all the variations in fitness noted to exist between subjects of different races and from different environments.

Vital capacity is correlated directly with the endurance time (11) but, although the Sinhalese male adult gives the longer mean endurance time, the Ceylon Tamil has the greater vital capacity (15).

Our physical correlations do help to explain why some groups of subjects, e.g. the Indian Tamils, have a high mean fitness index blood pressure but a low mean fitness index pulse.

It should be noted that all our subjects were examined in their own environment and, although these examinations were made during the so-called 'cool' season of the year, variation in environmental conditions was inevitable. It might be suggested that the variation in fitness indices, shown by subjects from the varying environments of Ceylon, was due to the variation in the atmospheric conditions under which the tests were performed. We have, however, been unable to detect any significant correlation between the fitness indices and the atmospheric temperature, the relative humidity and effective temperature (ranges of effective temperatures, 68° F. to 80° F.).

SUMMARY

Data obtained during the assessment of the physical fitness of 7000 Ceylonese subjects have been compared with the anthropometric characteristics of these subjects. Some significant correlations have been identified. The significance of these correlations in explaining the noted differences in fitness between subjects of different racial, environmental and economic groups is discussed.

APPENDIX A

Analysis of Variance (Fitness Index Pulse). A full analysis of the total variance has not been made. Our data are not homogeneous and many groups and sub-groups of our analysis of variance tables contain no observations. A partial analysis has been made using the data for the age groups 10 to 13 years, 14 to 16 years and 21 to 35 years for Sinhalese and Ceylon Tamil male and female subjects. In this case the variance can be divided as follows:

SOURCE OF VARIANCE	VARIANCE	DEGREES OF FREEDOM FOR ESTIMATE
Race	710	6
Sex	5000	3
Age	8620	2
Environment	1500	2
Residual	268	3218

Calculation of the simple variance ratio (F) for each source of variance gives the following values:

Race/Residual, $F = 2.650$ ($P < 0.05$ & > 0.01)

Sex/Residual, $F = 18.658$ ($P < 0.001$)

Age/Residual, $F = 32.16$ ($P < 0.001$)

Environment/Residual, $F = 5.596$ ($P < 0.01$ & > 0.001)

All these are significant and the relatively greater importance of age and sex in determining the variance of the fitness index (pulse) of a population is well illustrated.

Analysis of Variance (Strength). As many of the possible groups and sub-groups in the classification of our data are lacking, a full analysis of variance has not been possible. A partial analysis has been made, using the strength data for the age groups 10 to 13 years, 14 to 16 years and 21 to 25 years for Sinhalese and Ceylon Tamil male and female subjects. In this case the variance can be divided as follows:

SOURCE OF VARIANCE	VARIANCE	DEGREES OF FREEDOM FOR ESTIMATE
Race	1000	6
Sex	18,170	3
Age	8450	2
Environment	1433	2
Residual	300	2788

Calculation of the variance ratios (F) gives:

Race/Residual $F = 3.35$ ($P < 0.01$ & > 0.001)

Sex/Residual $F = 60.57$ ($P < 0.01$)

Age/Residual $F = 28.15$ ($P < 0.001$)

Environment/Residual $F = 4.77$ ($P < 0.01$ & > 0.001).

All these are significant and the greater importance of age and sex in determining strength is well illustrated.

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Effects of Active and 'Passive' Limb Movements Upon Respiration and O_2 Consumption in Man

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DESPITE EARLIER ATTEMPTS on the part of Haldane, L. J. Henderson, Winterstein, Hasselbalch and Gesell to explain the regulation of respiration upon a single basis, it has become apparent that the minute volume of breathing is the resultant of many factors operating concurrently in the same or opposite directions. "The most important discovery of the last century (in respiratory physiology) has been the realization that respiration is controlled not by reflexes alone, not by chemical stimulation of the medulla alone, but by the proper interaction of both factors. Respiratory alterations . . . cannot be explained by any single simple theory but only by a consideration of a number of known and probably many unidentified factors" (1).

More recently there has been an attempt to place this multiple factors concept upon a mathematical basis (2). However, the *quantitative* rôle played by each of these factors is still a controversial matter. This is particularly true of reflexes, stimulant to respiration, associated with movements of the limbs. On the one hand, Comroe and Schmidt (3) feel that though reflexes do arise from passive movements of the limbs, they play a relatively unimportant rôle in the regulation of respiration during any but very mild exercise because they produce only a mild hyperpnea, and do not provide for adjustment of pulmonary ventilation to the work done but only to the rate and extent of limb movement. Von Euler and Liljestrand have also produced evidence indicating that limb reflexes are relatively unimportant (4). On the other hand, Harrison *et al.* (5) believe that the "increase in ventilation produced by mild muscular exercise is reflex in origin." Asmussen and associates (6–8) have concluded that the increase in ventilation during light exercise is most likely due to reflexes from the working muscles. In addition, Gray (2) has expressed the view that, "This conclusion (that the limb reflexes play a negligible rôle in active exercise) is wholly unjustified. It has been reported that passive exercise of one leg in human subjects produces an average increase in ventilation of 40 per cent. If it can be assumed that the passive nature of the exercise prevents any change in metabolic rate it can be calculated that a considerable hypocapnia and alkalemia must have resulted. The reflex must have been so powerful that, acting alone, it should increase respiration 520 per cent. Contrary to the original conclusion, this analysis implies that the muscle reflexes may play a major rôle in mediating the respiratory response to exercise."

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The studies to be described were performed to determine more precisely the portion of the hyperpnea of muscular exercise that may be attributed to passive movements of the limbs.

METHODS

Healthy young adults, accustomed to laboratory procedures, served as subjects. They were resting, but not basal, at the beginning of each study. All test procedures were performed at least once upon each subject before measurements were made. Comparisons were made between the effects of active and 'passive' movements and between the effects of passive movements during inhalation of air and again of CO_2; in all cases, a steady state of breathing was attained (breathing air or 5% CO_2) before any movements were made. 'Passive' movements were made in two ways. In some subjects (supine), the arm or leg was grasped at the wrist or ankle; attempts were made to immobilize the upper arm or thigh during the manipulation. In other studies passive movements of both feet, legs and thighs were produced in subjects sitting upon a stationary bicycle. The subjects were instructed to relax with their feet in contact with the pedals while the latter were driven by an electric motor at a rate of 60 r.p.m. for periods of 5 minutes. The same subjects, after an appropriate rest period, performed active exercise at the same rate upon the same bicycle with minimal load (the chain connecting the ball bearing pedal sprocket to the rear wheel was disconnected). When 5 per cent CO_2 in air was breathed, this was supplied to the inspiratory valve from a high-pressure tank through an appropriate reducing valve and demand regulator. Respiratory minute volume was measured by conducting the expired air from a small face mask through the expiratory valve to a recording Tissot spirometer. Oxygen consumption and CO_2 production were measured over a 5-minute period by the open circuit method employing the Tissot spirometer and a Haldane gas analyzer.

RESULTS

The magnitude of the respiratory response to passive movements involving one to six joints is shown in tables 1 and 2. During passive movements of the forearm (6 subjects) respiratory volume increased 6.3 to 23.1 per cent; of one leg (5 subjects) 13.1 to 26.2 per cent; of one arm and leg simultaneously (4 subjects) 20 to 31 per cent; and of both feet, legs and thighs (10 subjects) —2.8 to 57.1 per cent.

The persistence of the response resulting from passive movements was tested in 7 subjects upon the bicycle by recording the volume of respiration each minute for 5 minutes. As a rule the hyperpnea was greatest during the first minute of movement and was maintained at a lower level thereafter. The mean values were: resting 8.7; during successive minutes of passive movements, 11.8, 10.8, 10.0, 10.8, 10.5 liters/minute.

The absolute increase in minute volume induced by passive movements was greater in every instance when these were performed during inhalation of 5 per cent CO_2 (table 1). However, the mean percentage increases, using resting ventilation during air or 5 per cent CO_2 inhalation as the base line, were 16.8 and 17.7 per cent.

In 9 subjects, it was found that the average increase in O_2 consumption was almost as great during passive movements (36.5%) as during active movements upon the bicycle against minimal resistance (40.0%). (Similar increases in CO_2 production were observed.) The average change in respiratory minute volume was only slightly greater during active movements (30.9%) as compared with passive motion (25.3%); in 5 of the 9 subjects the hyperpnea during passive movements exceeded that of active exercise. In general, changes in minute volume paralleled changes in metabolic rate. In 3 subjects, arterial

TABLE 1. EFFECT OF 'PASSIVE' MOVEMENTS UPON RESPIRATION OF NORMAL MEN BREATHING AIR OR 5% CO_2 IN AIR

SUBJECT	RESTING M.V. L/MIN.		% INCREASE IN M.V. DURING PASSIVE MOVEMENTS							
			Arm		Leg		Arm & leg		Feet, legs & thighs	
	Air	*5% CO_2*	*Air*	*5% CO_2*	*Air*	*5% CO_2*	*Air*	*5% CO_2*	*Air*	*5% CO_2*
S. M. H.	6.8	17.6	14.2	16.0	19.3	16.1	20.0	19.0		
H. M.	8.0	26.7	23.1	15.0						
S. H.	7.7	18.5	10.4	25.4	26.2	17.8	31.0	17.8		
R. P.	8.8	26.7	6.3	10.1	17.3	18.0	28.3	14.3		
W. F.	9.1	35.4	8.8	9.3	13.1	25.4	21.5	25.4		
B. K.	8.7	22.5	12.4	18.4	24.8	29.3				
R. B.	8.9	18.9							9.2	14.4
H. B.	6.9	17.1							0.0	10.2

blood samples were collected before and during passive movements of the limbs (bicycle); although the minute volume of respiration increased 6, 10 and 55 per cent, there was no change in arterial *p*H, CO_2 content or calculated pCO_2.

DISCUSSION

Previous studies have shown that passive movements of the limbs can lead to mild or moderate hyperpnea in dog, cat and man (3, 5). These investigators concluded that part or all of this hyperpnea was of reflex, rather than of humoral, origin because it was reduced or abolished by spinal cord section or spinal anesthesia but persisted when all vessels to and from the limb were occluded.

The present experiments were designed to determine the magnitude of the hyperpnea that can be produced in man by 'passive' movements of the limbs.

Deficiencies in the plan of previous experiments, which may have limited the full extent of the response, were that only one limb was moved at a time in the human experiments and that no provisions were made to maintain a constant arterial pCO_2 in order to ensure normal excitability of the respiratory center. In the present studies, an attempt was made to provide the most favorable conditions for the 'passive movement reflex' by producing simultaneous movement involving as many as 6 joints and at the same time maintaining or increasing the excitability of the respiratory center by inhalation of 5 per cent CO_2 in air.

The magnitude of the hyperpnea in this small series did not exceed that previously reported when only one leg was moved. Although the conditions of the two studies (rate and type of movement, position of subjects) were not identical, it was anticipated that more powerful effects would be elicited by

TABLE 2. EFFECT OF ACTIVE AND PASSIVE MOVEMENTS OF BOTH FEET, LEGS AND THIGHS UPON VENTILATION AND O_2 CONSUMPTION

SUBJECT	VENTILATION (L/MIN.)						O_2 CONSUMPTION (CC/MIN.)					
	Rest	Passive movts.	% Change	Rest	Active movts.	% Change	Rest	Passive movts	% Change	Rest	Active movts	% Change
P. F.	6.0	7.0	16.6	5.9	9.8	66.1	260	316	21.5	264	386	46 2
R. B.	8.2	11.4	39.0	8.5	11.2	31.7	244	387	58.0	252	404	60 3
M. G.	5.3	6.6	24.5	6.2	8.0	29.0	216	273	26.0	259	390	50 5
M. M.	9.3	9.1	−2.8	9.6	12.3	28.1	340	394	15 8	311	456	46 6
S. B.	11.5	14.3	24.3	11.5	13.1	13.9	321	500	55.7	329	398	20 9
G. N.	7.0	9.0	28.5	7.7	12.0	55.8	287	386	34.4	325	493	51 6
G. G.	8.4	10.1	20.2	8.7	9.4	8.0	295	388	31.5	299	348	16 3
N. R.	13.0	15.7	20.7	14.4	13.1	−9.1	356	489	37.3	373	408	9 3
L. C.	7.7	12.1	57.1	7.6	11.8	55.0	230	365	58.6	234	372	58 9

motion involving 6 joints simultaneously. Since the maximal effect noted in this study was an increase of 57 per cent, and since active muscular exercise is capable of increasing ventilation as much as 1100 per cent, it is apparent that *passive* movements do not play an important rôle in the production of hyperpnea in muscular exercise. This does not deny the existence of muscle or tendon receptors; activation of these by shortening of the muscle during its contraction may be a more potent stimulus than passive lengthening. However, simple passive movements involving the joint, or passive lengthening of muscle or tendon, do not seem to initiate any important respiratory reflexes.

Gray, in his calculations (2), greatly overestimated the importance of the limb reflexes because he assumed a passive nature of the movements which precluded any change in metabolic rate. Liljestrand and Stenstrom, in 1922, (9) reported that O_2 consumption of 2 subjects increased 45 and 32 per cent during passive movements of the limbs but this observation has not been

widely quoted. The present experiments, and those recently reported by Otis (10), have shown that passive movements, of the type produced, increased O_2 consumption almost as much as active exercise without load but at the same rate. The increase in O_2 consumption may arise from inability of the subject to suppress active contractions during the 'passive' movements, or may result from the activation of stretch receptors which reflexly increase muscle tone. The finding that metabolism increases with passive movements of limbs is of obvious importance to those concerned with problems of physical therapy. The demonstration that O_2 consumption and CO_2 production increase during passive movements does not, of course, negate the existence of a peripheral stretch reflex capable of influencing respiration.

SUMMARY

The hyperpnea produced by 'passive' movements of limbs in a man cannot account for more than a small fraction of the total hyperpnea caused by vigorous active muscular exercise; this is true even when the excitability of the respiratory center is maintained or enhanced by inhalation of 5 per cent CO_2. So-called 'passive' movements are accompanied by an increase in O_2 consumption approximately equal to that produced by active exercise at the same rate with minimal load.

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A Study of Carbon Dioxide Present in the Oral Cavity During Inspiration

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THE FOLLOWING EXPERIMENTS were planned to investigate possible gaseous exchange in the oral cavity during respiration. The conclusion reached was that there is no significant exchange, under the conditions of the experiments. The literature on the subject has been contradictory, and has been reviewed recently by Galdston and Horwitz (1) who, in their own experiments, found an average of 3.7 mm. Hg of CO_2 in periods of equilibration ranging from 2 to 40 seconds. The area explored by these investigators, however, covered the whole of the upper respiratory tract above the glottis, whereas the present series investigated the oral cavity alone, in an effort to eliminate the salivary secretions as a source of carbon dioxide.

An earlier communication (2) drew attention to the significant difference in carbon dioxide content obtained when comparing alveolar air collected under two different conditions. The first group was collected at the end of a normal expiration, without cooperation from the subject; the second group was similarly obtained, but after clearing the deadspace with a suction method. It seems reasonable to suspect that, if the gas in the area of the respiratory tract situated above the glottis is not completely replaced during a normal expiration, inspiration is likewise insufficient to replace all the deadspace air. Any residual gas might be confused, not only with glandular gas exchange, but also with variations in alveolar gas composition, and estimates of pulmonary function which are based on an assumption of unequal lung ventilation may utilize values which have not taken these factors into account.

The following experiments were planned to eliminate residual CO_2 as far as possible from the deadspace, to try and estimate the magnitude of this

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contamination, and to detect any subsequent change in gas composition, after removing the contamination, on the assumption that a change would represent equilibration with glandular secretions. Carbon dioxide was selected for analysis as the most diffusible of the respiratory gases and therefore the one most likely to evade clearance by the normal methods.

APPARATUS AND PROCEDURE

Samples of respiratory gas were collected from the oral cavity at the end of inspiration by means of a modification of the alveolar air sampler used in the investigation referred to above (2). This is illustrated in the accompanying diagram. Briefly, the principle of the apparatus is that by turning a tap through

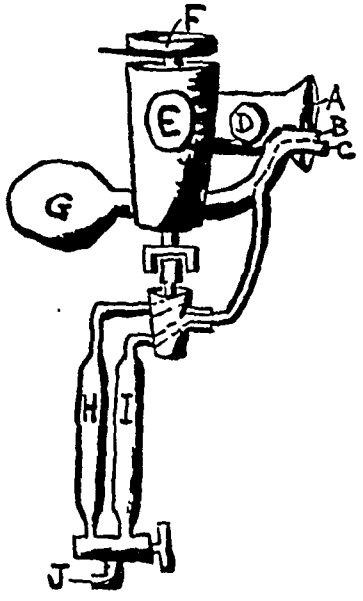

Fig. 1. *A*, mouthpiece; *B*, suction tube; *C*, sampling tube; *D*, space for expiratory valve if required; *E*, air inlet-outlet; *F*, tap; *G*, rubber bulb; *H*, evacuated barrel for clearance; *I*, evacuated barrel for sample; *J*, to mercury reservoir.

one full rotation at any desired moment in the respiratory cycle, a series of channels are successively utilized, culminating in the collection of a sample of respiratory gas. First, the connection with the outside air *E*, (which is open only at one position of the tap in its full rotation) is closed. Immediately after this a second inlet is brought into play; in the previous experiments, when the object was the sampling of alveolar air, this was connected with a rubber bulb, *G*, which was used to partially evacuate the upper deadspace, but here it was used to introduce a stream of air, when required, for washing out the oral cavity. Thirdly, a specially designed vacuum sampling tube, *H*, *I*, comes into action through a tube leading to the mouth, and receives the sample. Finally, with completion of the full rotation, the air passage is opened up again, and the subject is able to continue normal breathing.

Two modifications were made to the above apparatus for the present purpose. An expiratory valve was fitted just distal to the mouthpiece, at *D*, in

order to permit the washing-out procedures. The tube for sampling, *C*, was extended so as to lie on the tongue.

About 5 cc. of gas were collected at each experiment, and analyses were carried out by the Scholander method.

The total deadspace of the apparatus was 25 cc., but only 10 cc. was in communication with the oral cavity at the time of sampling. An average amount of gas held in the mouth during the experiment was 50 cc. Assuming a complete mixing with this 10 cc., there would be a maximum possible reduction, by dilution, of some 17 per cent. This is probably negligible since for the concentration observed it would imply an error of only .01 per cent, which is beyond the accuracy obtainable.

In the experiments the subject was seated, a noseclip was applied, and a rubber mouthpiece placed in position. Normal breathing was carried out with the tap open. At the end of an inspiration the subject swallowed immediately, and remained in that position with the breath held for the required time. At the end of this pause the rotation of the tap was completed; this automatically collected a sample and returned the outlet, *E*, to room air. Samples were collected at the end of normal inspirations and also at the end of deep inspirations. These were taken at varying times after the oral cavity had been sealed off from the rest of the respiratory tract by the act of swallowing, the back of the tongue being consciously kept in a position to maintain this seal.

RESULTS

The experiments were divided into four groups: *a*) Samples of air were collected from the mouth at intervals of from 2 to 30 seconds, at the end of a normal inspiration and also at the end of a deep inspiration. In this series, 8 samples taken at the end of normal inspirations showed a mean value of .27 per cent CO_2, and 9 taken at the end of deep inspirations showed a mean of 0.3 per cent CO_2.

b) In the next series the oral cavity was washed out by means of a rubber bulb of 180 cc. capacity, filled with room air (which showed at analysis .04 per cent CO_2), immediately after a deep inspiration and swallowing maneuver. For this purpose the bulb normally used in the collection of alveolar air was used, with its valve reversed to allow blowing instead of suction. Air was washed into the mouth from the bulb and passed out through the expiratory valve at *D*. In 8 experiments with breath holding varying from 15 to 35 seconds, values ranging from .13 to .25 per cent of CO_2 were found, with a mean of .18 per cent for the series.

c) The washing out in the previous group having evidently removed the carbon dioxide which remained in the oral cavity at the end of the deep inspiration, it was decided to wash out the mouth more completely by means of a stream of air, introduced at the point *G* after removing the bulb. The results

of this series are shown in table 1. There was no increase in the amount of CO_2 in the oral cavity at any period up to 30 seconds after the washing-out procedure.

The possibility that the introduced stream of air might build up to a high pressure during the time that the tap was turned off and thus wash out the

TABLE 1. SAMPLES OF AIR TAKEN FROM ORAL CAVITY AT END OF DEEP INSPIRATION, AFTER SWALLOWING, AND AFTER WASHING OUT MOUTH WITH A GENTLE FLOW OF AIR FROM A CYLINDER OF COMPRESSED AIR[1]

TIME[2]	CO_2	TIME[2]	CO_2
sec.	%	*sec.*	%
5	.02	25	.02
5	.03	25	.03
5	.06	30	.08
15	.06	30	.12
15	.01	Mean.....	.05
20	.07	Room air.....	.02
20	.01	Cylinder Air.....	.01

A further group of 14 similar observations had a mean value of .08% CO_2.

[1] This flowed through a wash bottle. [2] Times measured from the end of the washing out procedure.

TABLE 2. PERCENTAGE OF CO_2 IN SAMPLES OF AIR TAKEN FROM ORAL CAVITY ON ONE DAY, AT END OF DEEP INSPIRATION, AFTER SWALLOWING

EXPERIMENT[1]	ONE SEC.	30 SEC.	EXPERIMENT[1]	ONE SEC.	30 SEC.
1	.27	.24	7	.08	.14
2	.17	.24	8	.07	.12
3	.18	.22	9	.12	.10
4	.08	(.59)[2]	10	.13	.15
5	.15	.07	11	.11	.11
6	.11	.14	Mean.....	.13	.15

[1] Each experiment consisted of 2 samples, one at 1 sec. and the other at 30 sec. [2] The bracketed figure was excluded, as the swallowing maneuver was not satisfactory.

CO_2 from the saliva, before the stream was admitted, was obviated by introducing the air-supply tube only when the aperture at *G* was open, and the expiratory valve at *D* prevented any possible rise in pressure. The stream of air was so slight as to be barely perceptible, and was shut off at the moment that timing began. The air passed through a wash bottle for humidification and was allowed to circulate gently round the mouth through the tube *B*. The anterior part of the tongue was moved about to facilitate this, and the cheeks stretched by pulling backwards on the rubber mouthpiece, which had a large flange. After 5 seconds the tap was rotated a little further, thus shutting off the air stream, and after a pause of the required number of seconds the sampling was completed. Care was taken to ensure that as much saliva as possible

was present in the mouth at each experiment. Any convenient method of delivery of air would serve in the place of the compressed air cylinder used, as was shown by the reduction in carbon dioxide attained when using even such a small source as the 180 cc. rubber bulb referred to above.

d) The final group was taken with especial regard to distension of the cheeks by pulling back on the rubber mouthpiece. The flange on the mouthpiece was big enough to obviate the possibility of leaks. After a deep inspiration and swallowing, a sample was taken immediately and a second sample was taken 30 seconds later. The results are shown in table 2. There is clearly no evidence of carbon dioxide exchange during the interval between the first and the second sample of each pair.

DISCUSSION

Evidently no significant gaseous exchange occurred in the oral cavity during the experiments described. Values in the neighborhood of 0.3 per cent of CO_2 were found in the oral cavity at the end of a normal or deep inspiration, unless special measures were taken to ensure a complete change of air in the mouth. When these precautions were taken, the amount of CO_2 was found to diminish in proportion to the efficiency of the measures used.

From this it might be deduced that a small but important amount of CO_2 remains in the oral cavity, even at the end of a deep inspiration. In this connection it may be mentioned that Krogh and Lindhard, as long ago as 1914, were convinced that in order to wash out the deadspace completely, an expiration of about three times the volume of the deadspace is required (3). Haldane (4) found that an expiration of about 1500 cc. would be needed to obtain a sample of undiluted alveolar air at the end of an inspiration of 2000 cc.

It seems likely that the source of this residual CO_2 was not from below the glottis. However, the possibility must not be excluded that a small portion of inspired air, possibly contaminated from the deadspace below the glottis, was sucked up by the swallowing procedure. It is difficult to devise any simple experimental procedure which will demonstrate this point, but it was felt that the posterior part of the tongue constituted an efficient seal, as indeed was proved during the equilibration time, when no rise in CO_2 occurred during breath-holding. It may be stated therefore with some confidence that there is no reasonable doubt as to the source of contamination, and that the CO_2 was present in the oral cavity at the time of swallowing.

The salivary glands did not contribute CO_2, at least during the 30 seconds allowed for equilibration, and would not be of importance therefore during ordinary respiration.

SUMMARY

A total of 73 estimations of the carbon dioxide present in the mouth at the end of inspiration was made on one individual, after allowing up to 30

seconds of equilibration with the salivary secretions. No evidence of gas exchange was found, but a small residuum in the neighborhood of 0.3 per cent of CO_2 was found at the end of a normal or deep inspiration, if no measures were taken to wash out the mouth before sampling.

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Variability of Heart Rate in Relation to Age, Sex and Stress[1]

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THE MAIN PURPOSE of the present study was to observe the degree of correlation between age and heart rate variability. This measure has been employed in studies of emotion (1, 2) and with the development of the recording cardiotachometer (3) observations on heart rate variability will probably come into more common use. For methodological reasons it is important to know whether this measure correlates significantly with age. A further purpose was to study the influence of sex and respiratory phase upon heart rate variability.

METHODS AND SUBJECTS

Present data were derived from two separate physiological investigations in which psychiatric patients were observed under standard conditions of stress. In each of these studies, heart rate was recorded, by means of the electrocardiograph, as part of a battery of physiological measurements. Respiration was recorded with a pneumograph and tambour. The stress situation involved a series of 12 pain stimulations of fixed order and intensity, presented by means of a Hardy-Wolff thermal stimulator (4). Details of the stress procedure have been described in previous reports (1, 5). Heart rates were determined from 60 samples of 3 beats each, measured at set intervals during the test. The samples were taken immediately before, during and after pain stimulation, and before and after standard questioning. They were purposely made brief (3 beats), in order to facilitate observation of transient changes. Heart rate variability was determined by calculating the standard deviation (S.D.) of the 60 measurements. A similar procedure has been employed by Fleisch and Beckmann (6) and Whitehorn and Richter (2).

The procedures employed in our two investigations differed in certain details: *1*) The experimental situation was the same in both, but in the second study the stress was probably increased by the addition of a nearly continuous blood pressure recording with the Lange instrument (7). *2*) The heart rates in the first investigation, which we shall designate as the '1947' study, were measured without regard to the phase of respiration, while in the second study

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('1948'), they were measured only during the expiratory phase of respiration. 3). In the 1947 study, three measurements were made around the time of pain (before, during and after); in the 1948 study, only two were made around the pain stimulus (immediately before and during) and the third was replaced by a measurement made 20 seconds before stimulation. The subjects were unselected patients from a psychiatric institute attached to a general hospital. There were no chronic institutionalized psychotics in this group. There were 75 patients in the 1947 group, of whom 23 were male and 52 female, with ages ranging from 13 to 63. The 1948 group contained 59 patients, 26 male and 33 female, with ages ranging from 17 to 62. Data on 21 normal controls, 7 males and 14 females aged 18 to 39 were also taken.

TABLE 1. FACTORS OF AGE AND SEX IN HEART RATE VARIABILITY

	PATIENTS						NORMAL CONTROLS
	1947 Group			1948 Group			
	Male	Female	Total	Male	Female	Total	
No. of cases	23	52	75	26	33	59	21
Correlation of H.R. variability with age	−0.40[2]	−0.63[1]	−0.60[1]	−0.54[1]	−0.64[1]	−0.59[1]	−0.47[1]
Mean H.R. variability	4.54	5.06	4.90	4.10	4.93	4.56	4.65
S.D. of H.R. variability	1.51	1.82	1.61	1.17	1.32	1.32	1.35
Sex difference, *P* value		0.20			0.02		

[1] Product-moment correlation coefficients significant at 1% level of confidence.
[2] Coefficients significant at 5% level.

RESULTS

Table 1 shows the data relating heart rate variability to age and sex. There was a negative correlation between age and heart rate variability in both series of cases and for both sexes. This means that heart rate variability decreased with increasing age. The magnitude of the correlation with age was remarkably similar in both series, considering the differences in the procedures employed in these studies. Figure 1 shows the linear functions derived from the regression equations for each set of data, together with the actually observed mean points. From the relatively good agreement between the predicted and observed data it appears likely that heart rate variability decreases with age in a linear fashion, at least over the age range studied.

In both series of patients, the heart rate variability of the female group showed a somewhat higher correlation with age than did that of the male group. Also the mean variability scores tended to be higher for the female group. This sex difference was reliable at the 2 per cent level of confidence for the 1948 group, but not reliable for the 1947 group. Since the mean ages of the

male and female groups were approximately equal in both studies, it appears likely that females show a somewhat higher heart rate variability than males.

In order to determine the effect of respiratory phase differences on our measurements of heart rate, the records of 38 patients (comprising one half of the 1947 group) were analyzed separately for the inspiratory and expiratory phases of respiration. The correlation between the respiratory phase difference in heart rate and the variability score (S.D.) yielded a positive coefficient of 0.57. This indicates that heart rate variability was higher in those patients in whom the respiratory phase difference was greater. The correlation between respiratory phase difference and age was −0.46, indicating that the respiratory phase difference decreased with age. However, all measurements in the 1948 series were made in the phase of expiration; since the same correlation with age was obtained under these conditions as when respiratory phase was not controlled, it appears that the relationship between heart rate variability and age is not dependent upon variations in the heart rate correlated with respiratory phase. There was no significant correlation between heart rate and heart rate variability.

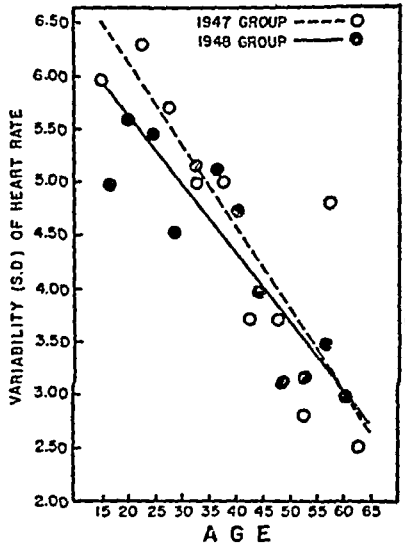

Fig. 1. CURVES SHOWING RELATIONSHIP between heart rate variability and age. The smooth curves are taken from regression equations based on the correlation coefficients.

Data on 21 normal controls, taken together with the 1948 patient series, indicate that heart rate variability decreases with age in normals as it does in psychiatric patients. In this small group, with the relatively narrow age range of 18 to 39, the correlation between heart rate variability and age was −0.47.

DISCUSSION

The finding that heart rate variability decreases with age raises questions concerning the physiological mechanisms involved and the manner in which these may vary with age. Pertinent data on these points are provided by Crawford's (8) study of the effect of atropine on the heart rate. Crawford found that the increase in heart rate following injection of atropine was greatest in the age group from 20 to 30 and that this effect became smaller with increasing age. He presented a curve, relating the effect of atropine to age, which closely resembles the curve for heart rate variability and age obtained in this study. It thus appears that heart rate variability, as measured here, is probably related to the effect of atropine as measured by Crawford.

Crawford's interpretation of his results was that, with age, there is both a decrease in tonicity of the cardio-inhibitory center and a lower intrinsic rhythm of the heart. Both Crawford's study and the present one showed that pulse rate does not vary significantly with age. Since heart rate is considered to result from a balance between vagal and sympathetic tone, and since Crawford's data show that vagal tone decreases with age, there must also be a diminution of sympathetic tone with age to account for the maintenance of a relatively unchanged heart rate. With reduction in the tonicity of the antagonistic impulses acting upon the heart, it would be anticipated that the degree of lability would decrease with age. Furthermore, under conditions of stress, which are conducive to autonomic lability, this relationship might perhaps be accentuated so that the older individual would manifest considerably less variability than the younger.

SUMMARY

The results of this study indicate that age, sex and respiratory phase are factors to be taken into account in investigations of heart rate variability. Heart rate variability under stress appears to decrease linearly with age, a finding which may be explained in terms of diminished autonomic nervous system influences, both vagal and sympathetic, with increasing age.

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Effects of Environmental Heat Stress and Exercise on Renal Blood Flow and Filtration Rate

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STUDIES OF THE RENAL CIRCULATION during exercise have been carried out by a number of investigators and the results have recently been reviewed by Herlitzka (1) and by Chapman *et al.* (2). In general, it is agreed that the total renal plasma flow is reduced during exercise but the effect on glomerular filtration rate is not well defined. Barclay *et al.* (3) report a fall of 45 per cent in filtration rate following exhausting exercise, and White and Rolf (4) report little or no change during light exercise. The ability of the kidneys to shunt blood to other tissues in exercise suggests that they may play a similar role when other stresses are imposed on the organism. Since heat stress on men may cause profound strains on the circulation, especially when it is combined with work, the present study has been planned to investigate the effects of a moderate degree of exercise on the renal plasma flow and glomerular filtration rate in both cool and hot environments.

PROCEDURE

The experimental subjects were five adult males, all in excellent physical condition with no evident renal pathology. All subjects were well acquainted with the experimental procedures of venipuncture, exercise on the treadmill and hot environmental temperatures, thus reducing to a minimum any source of error due to apprehension.

Sodium para-aminohippurate (PAH) was used for the determination of renal plasma flow, and mannitol for measuring glomerular filtration rate. The method of Smith *et al.* (5) was used for the analysis of PAH in plasma and urine. The analytical method as described by Barker and Clark (6) was used for the determination of mannitol. Our subjects were prepared for each test by having them omit the meal preceding the test. One hour before the test, they drank 800 to 1000 cc. of water to produce diuresis. In order to maintain the diuresis, the subjects drank 200 to 300 cc. of water during each 20-minute period of the

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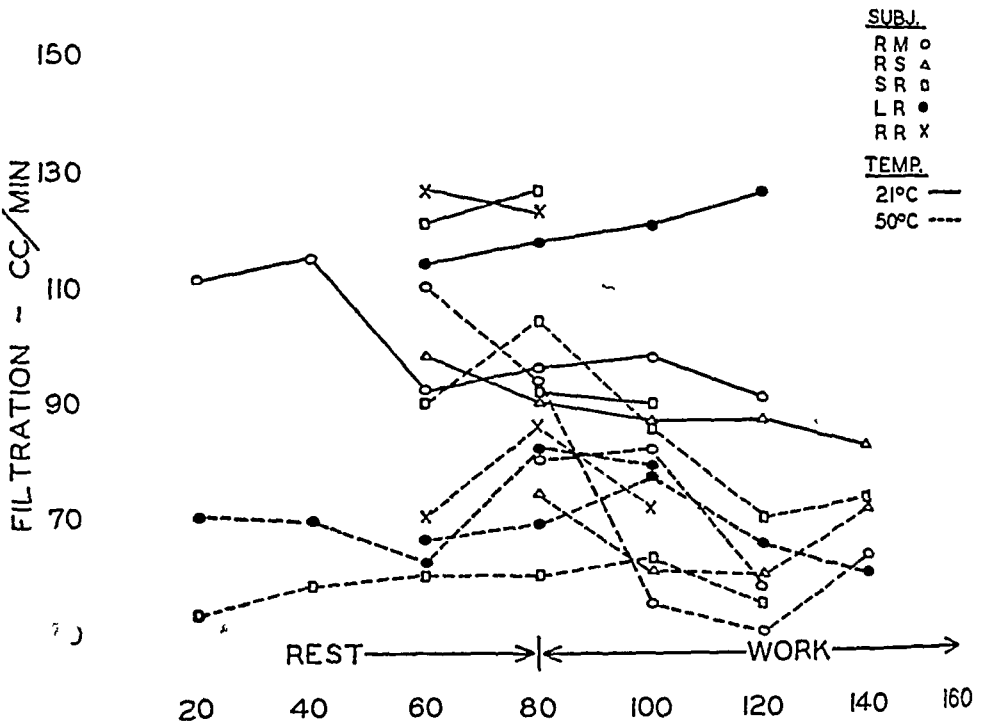
[1] This study was supported by a grant from the Division of Research Grants and Fellowships, National Institutes of Health, U. S. Public Health Service.

at rest, the mean values for the exercise periods being 102, 103 and 101 cc. per minute respectively. When the resting subjects were exposed to the heat, the mean glomerular filtration rate was 84 cc. per minute, a decrease of 21 per cent from the resting level in the cool environment. In the first exercise period in heat, the filtration rate fell 15 per cent from the resting level, the mean being 70 cc. per minute. During the second and third exercise periods, the observed filtration rates were 25 and 24 per cent respectively, below the resting level in the heat.



During exercise in the cool environment, the mean values of total plasma flow obtained in our subjects are in accord with those obtained by Chapman *et al.* (2) for the same grade of work. Although their percentage decreases are not

TABLE 1. EFFECTS OF EXERCISE AND HEAT STRESS ON THE MEN'S RENAL BLOOD FLOW AND RENAL FRACTIONS. EXERCISE AND ENVIRONMENTS DESCRIBED UNDER PROCEDURE

	BLOOD FLOW		
	Min. Vol. *l/min.*	Renal *cc/min.*	Renal Fraction %
Rest in cool environment	4.8	1250	26.0
Rest in heat	4.5	775	17.2
Exercise in cool environment	12.1	524	4.3
Exercise in heat	11.0	496	4.5

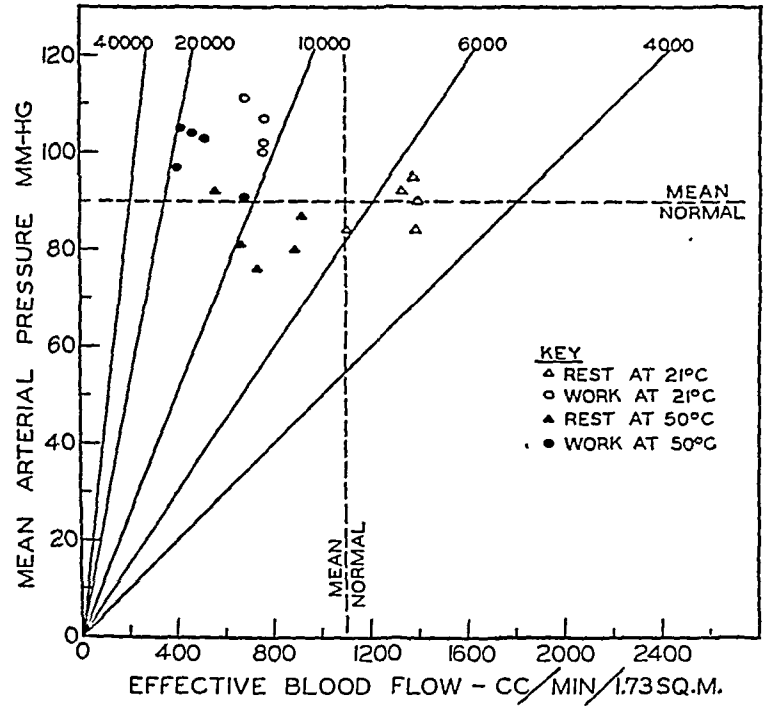


Fig. 3. Relationship between mean arterial pressure and renal blood flow. Diagonal lines originating from o indicate effective vascular resistance. Points on graph represent mean calculated resistances for each of the subjects during each condition studied.

as great as ours, the main discrepancy is in the mean resting level, ours being somewhat higher than theirs in rest and falling to the same level as theirs in exercise.

The results of this study indicate only a slight decrease of no statistical significance in glomerular filtration during exercise in the cool environment. White and Rolf (4) also observed no significant decrease in filtration rate during

light exercise. The average filtration fraction in our subjects at rest was normal but was significantly elevated during exercise. This is in accord with the results of Barclay *et al.* (3). When the subjects were at rest in the heat, the glomerular filtration rate decreased even though the total plasma flow was approximately the same as during exercise in the cool environment. This resulted in a higher filtration fraction at rest in the heat than was observed in the cool environment. While exercising in the heat, there was a further decrease in the filtration rate. The filtration fraction, however, was elevated to the same level as it was during exercise in the cool environment.

In order to determine the renal fractions of our subjects, cardiac output at the two metabolic levels was assumed from the data of Robinson (12), Christensen (13), Dill (14) and Cournand (15) on male subjects at the same metabolic levels. Cardiac output of the men in the heat was assumed from the data of Asmussen (16). The resultant renal fractions obtained are shown in table 1. There was a significant decrease in the renal fraction when the resting men changed from the cool environment to the heat. Associated with the increased cardiac output and lowered renal blood flow during exercise there was a large decrease in the renal fraction when the men worked in either environment.

The resting filtration fractions of our subjects in the hot and cool environments are within the reported normal limits although in the heat they are definitely higher than the fractions obtained in the cool environment. This would indicate an increase in the tone of the efferent arterioles, thus maintaining filtration pressure since no significant change in systemic blood pressure was observed at rest in the heat. The data indicate a practically parallel decrease in plasma flow during exercise in the cool and hot environments as well as identical increases in the filtration fraction; consequently it would seem that the mechanism producing the fall in renal blood flow during exercise probably operates regardless of the resting plasma flow.

Calculating and plotting the intrarenal resistances after the method of Lauson (17), we observed that at rest in the cool environment, the average resistances for each subject are within the reported limits of 4,000 to 10,000 absolute units (fig. 3). At rest in the heat, the intrarenal resistances are higher than those in the cool environment although, except for one subject, they are within the normal limits reported by Lauson. This elevation in resistance plus the rise in filtration fraction would support the idea that an increase in efferent arteriolar tone may be the cause of the reduction in renal blood flow. During exercise, both in the cool and hot environments, the intrarenal resistances are definitely in the zones of increased resistance (fig. 3). It seems probable from the low renal fractions, the elevated filtration fractions and the high intrarenal resistances, that the mechanism for the reduction of renal blood flow during exercise is a constriction of the efferent arterioles.

SUMMARY

Renal plasma flow and glomerular filtration rate were determined on five normal male subjects at rest and during moderate exercise on the treadmill (3 m.p.h. up a 5% grade) in both a cool (21° C.) and a hot environment (50° C.). Sodium para-aminohippurate and mannitol respectively were used for the determinations.

In the cool environment the mean renal plasma flow of the resting men was 695 cc. per minute and it dropped 42 per cent during exercise in the same environment. At rest in the hot environment the mean renal plasma flow was 426 cc. per minute. Exercise in the heat caused a decrease of 36 per cent from the resting level. In the cool environment the glomerular filtration rate of the men at rest averaged 108 cc. per minute and exercise in this environment did not significantly alter it. In the heat the average filtration rate of the resting subjects fell to 84 cc. per minute and when they exercised there was a further decrease to 70 cc. per minute.

Both exercise and exposure to heat stress caused the renal fraction to decrease and simultaneously caused increases in the intrarenal resistance and the filtration fraction.

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Enzyme Studies on Human Blood. VI. The Prothrombin Content of Plasma Stored up to Six Years[1]

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THE QUESTION OF THE STABILITY of prothrombin in stored human plasma is of importance, both experimentally and clinically, and therefore has been a subject of considerable investigation in recent years.

The prothrombin contents of blood or liquid plasma stored for various periods at ordinary refrigerator temperature as determined in percentage of normal by the one-stage technic (1, 2) according to various investigators are: 14 per cent, 3 weeks (3); 40 per cent, 3 weeks (4); 40 per cent, 5 weeks (5); 55 per cent, 7 weeks (6); 40 per cent, 17 weeks (7). Alexander and DeVries (8) employing the one-stage technic with barium sulfate plasma as a diluent found 180 per cent, 0 days; 110 per cent, 3 to 10 days; 210 to 294 per cent, 17 to 49 days; and 118 per cent, 54 days. In the same study, 4 per cent prothrombin was found by the unmodified one-stage technic in plasma stored for 54 days. Another investigator (9) reports 30 per cent prothrombin and no clot formation upon addition of calcium and thromboplastin in 5-month-old plasma. Somewhat higher results on liquid plasma stored for various periods at 3 to 5°C. have been obtained by the two-stage technic (10): 61 per cent, 3 weeks (3); 50 per cent, 3 weeks (4); 20 per cent, 8 weeks (11). With a two-stage technic (12) modified by the addition of Ac-globulin the following results were obtained on stored citrate plasma: 100 per cent, 8 weeks; and 50 per cent, 17 weeks (11). The results reported for prothrombin in stored frozen plasma are: 85 per cent, 7 weeks, one-stage technic (6); 100 per cent, 17 weeks, modified two-stage technic (11); and 40 per cent, 6 months, one-stage technic (13). With dried plasma variable prothrombin results are also reported: 20 per cent, 7 weeks, one-stage technic (6); and no change in 6-week-old plasma stored at 5°C. as compared to 3-day-old pooled plasma at the same temperature with the one-stage technic (14).

It is apparent from the foregoing that wide discrepancies exist even among investigators employing the same technic in the study of prothrombin stability in plasma stored up to 6 months. Reported here are plasma prothrombin results obtained by two different methods on 4 liquid samples stored up to 6 months; one frozen sample stored for 15 months; and 8 dried samples[1] stored from 48 to 72 months. Both technics have been described in detail in a previous communication (15). The new homologous isolation technic is based on the low temperature-low ionic strength alcohol removal of fibrinogen as Fraction I (16), and the subsequent isoelectric precipitation of the prothrombin fraction.

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[1] Dried plasma was processed from blood obtained from volunteer donors enrolled by the American Red Cross.

The thrombin technic is a modification of the two-stage procedures of Warner, Brinkhous and Smith (10), and Ware and Seegers (12).

DESCRIPTION OF SPECIMENS

Liquid Plasma. The 19-hour-old sample was collected by the University Hospital Blood Bank and processed in this laboratory. The 4- to 6-month-old samples were obtained from bank whole blood approximately 2 weeks old.

Frozen Plasma. Approximately 500 cc. of blood was collected from each of 4 normal adult males. The sterile citrate whole blood was then delivered to this laboratory where centrifugation at + 1°C. was begun within 30 minutes after venipuncture. The 4 samples were then pooled and stored in a −25°C. refrigerator.

Dried Plasma. The age of each preparation was calculated from the 5-year expiration date on the Standard Army and Navy Package. The dried plasma was reconstituted with 0.1 per cent citric acid to the volume of the 'original normal plasma,' as indicated on the label. All plasma specimens were sterile. With the exception of dried plasma, prothrombin results were corrected for anticoagulant dilution, about one volume of 4 per cent sodium citrate for every 10 volumes of blood. This study involves plasma samples representing more than 100 healthy adults whose histories, physical examinations and laboratory tests qualified them as blood donors.

DETERMINATION OF PROTHROMBIN

The *p*H of each plasma sample was taken with a glass electrode electrometer. For our isolation technic buffered alcohol was prepared so that the *p*H of the resulting alcohol-plasma mixture was 7.2 ± 0.2. In our thrombin technic, particular attention was given to the buffering of the defibrinating reagent so that the *p*H of the plasma-thrombin mixture was between 7.0 and 7.4.

RESULTS

The prothrombin results obtained by two technics on stored plasma are recorded in table 1. Identical results were obtained when fresh normal pooled plasma was added to activation mixtures.

DISCUSSION

The data, in the present work, demonstrate conclusively that prothrombin is exceedingly stable in dried plasma stored 4 to 6 years at various temperatures, and in frozen plasma stored 15 months at −25°C. Our results generally confirm those of Fahey, Ware and Seegers (11) on 4 months frozen plasma; and of Kazal and Arnow (14) on dried plasma stored 6 weeks at 5°C. The findings on liquid plasma stored 4 to 6 months at 3 to 5°C. are in agreement with those of Drew and Scudder (7) who reported 40 per cent remaining after 4 months;

and of Fahey, Ware and Seegers (11) who found approximately 50 per cent after 4 months with a two stage technic modified by the addition of Ac-globulin. However, in all of the present studies the addition of fresh pooled normal plasma to activation mixtures did not increase the prothrombin level. It is emphasized that the aged liquid plasma was obtained from outdated bank whole blood. Therefore, no definite conclusion can be reached at this time as to the degree of stability of this type of plasma.

TABLE 1. PROTHROMBIN RESULTS OBTAINED BY TWO TECHNICS ON NORMAL PLASMA OF DIFFERENT TYPES AND AGES

TYPE OF PLASMA	STORAGE		NO. PERSONS REPRESENTED IN SAMPLE	PROTHROMBIN RESULTS			
	Age	Temperature		Isolation Technic		Thrombin Technic	
		°C		*Units/cc.*	*% normal*	*Units/cc.*	*% Normal*
Liquid	15.0 min.	0–1	24[2]	82.4	100.0	110.0	100.0
	19.0 hr.	3–5	1	84.8[1]	102.9	97.3[1]	88.4
	3.7 mo.	3–5	8 (pool)	35.8	43.4	34.8	31.6
	5.5 mo.	3–5	8 (pool)	39.4	47.8	31.2	28.4
	6.0 mo.	3–5	8 (pool)	38.0	46.1	32.8	29.8
Frozen	15.0 mo.	−25	4 (pool)	78.8[1]	95.6	76.0[1]	69.1
Dried	48.0 mo.	Variable, usually, room temperature	ARC pool: more than 8 in each sample	59.5[1]	72.2	77.0[1]	70.0
	49.0 mo.			50.4[1]	61.2	71.8[1]	65.3
	49.0 mo.			61.8[1]	75.0	90.5[1]	82.3
	49.0 mo.			66.1[1]	80.2	93.2[1]	84.7
	68.0 mo.			57.1[1]	69.2	85.8[1]	78.0
	71.0 mo.			71.8[1]	87.1	91.5[1]	83.2
	72.0 mo.			68.0	82.5	88.0	80.0
	72.0 mo.			74.8	90.8	88.8	80.7
Mean.....	59.8 mo.			63.7	77.3	85.8	78.0
±S.D.....	11.8 mo.			8.1	9.8	7.5	6.8
C.V.%.....	19.8 mo.			12.6	12.7	8.8	8.8

[1] Average of duplicate analysis.

[2] Prothrombin results represent a mean of analysis on 24 normal individual specimens and were previously reported (15).

Several factors must be considered to account for the results obtained in the present study. First, all of the samples studied were sterile. Fahey, Ware and Seegers (11) attribute possible bacterial action as an explanation for their observation of diminishing prothrombin level after 2-month storage at 3 to 5°C. Second, careful *pH* studies were done on all samples. This is particularly important in processed and/or stored plasma in which the *pH* variations are greater than in fresh plasma. Since the thrombin-fibrinogen reaction is retarded in plasma above physiological *pH*, false low prothrombin results would be obtained on alkaline plasma, without prior neutralization, with the one-stage (1, 2),

two-stage (10, 12) and thrombin (15) technics. Similar misleading results would be obtained with the isolation technic (15) if careful *p*H control is not maintained; incomplete removal of fibrinogen as Fraction I would cause at least the partial inactivation of the thrombin formed. Third, standardized reagents were employed throughout this study. According to our experience it is essential to re-evaluate reagents when a prothrombin technic is applied to the study of plasma which varies from the *p*H, anticoagulant, etc. specified by the author of the procedure. For example, it does not necessarily follow that the calcium reagent optimal for fresh oxalate plasma, as established by Quick (1, 2) for the one-stage technic, would be adequate for stored citrate plasma. The 2.5 times excess thromboplastin and the 0.025 M calcium solutions employed for fresh plasma analysis in the previous study (15) were again titrated and found suitable for stored plasma with both technics.

Therefore, the high values for prothrombin in stored citrate plasma obtained in the present study is attributable primarily to the application of technic, i.e. careful *p*H studies and standardization of reagents, rather than to any particular analytical technic. Evidence for this is demonstrated by the comparable results obtained by two different procedures. Moreover, for some time Fraction I and crude prothrombin have been prepared from 2-liter lots of surplus liquid and dried plasma in this laboratory for its studies on coagulation. The principle of the preparative procedure is identical with that of the analytical isolation technic. Crude prothrombin powder in yields compatible with the analytical results have been obtained consistently even from aged liquid plasma obtained from outdated whole bank blood.

SUMMARY

Prothrombin was determined in various types of stored citrate plasma by the new isolation technic and also by the thrombin technic, a modification of the two-stage procedure. The results in percentages of that found in fresh normal plasma by the two technics are respectively as follows: 15 months frozen plasma, 95 per cent and 69 per cent; 4 to 6 years dried plasma, 77 per cent and 78 per cent. It is concluded that frozen and dried plasma, which have been processed within a short time after venipuncture and then stored for a considerable length of time, are adequate sources of prothrombin for transfusion and investigative purposes.

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Relationship between Leg Strength, Leg Endurance and other Body Measurements

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THE IMPORTANCE of leg strength and the ability to exert constant force in the event of mechanical failure were considered important factors in the selection of heavy bomber pilots for World War II. This study was made at the AAF School of Aviation Medicine, Randolph Field, Texas, in an attempt to determine whether height and weight standards for heavy bomber pilots could be reduced without materially modifying leg strength and leg endurance.

No literature was found which described a method of measuring the forceful extension of the leg and hip with the subject in a sitting position, nor was a method found for measuring the amount of time a predetermined amount of force could be exerted. Thus, it was necessary to design and construct special apparatus and test procedures that were considered to be sufficiently reliable for use.

The study was divided into two parts. In Part I, a total of 515 potential pilots in the following categories were used as subjects: *group 1*, 163 aviation students; *group 2*, 175 officers (returned combat bombardiers and navigators undergoing preflight training); and *group 3*, 177 aviation cadets in preflight training. In Part II, 75 pilots, *group 4*, undergoing continuation training were used as subjects.

Throughout this study the term 'leg strength' applies to the maximum forceful extension of the leg and hip against the resistance furnished by the dynamometer. Leg strength was measured in pounds. The term 'leg endurance' refers to the amount of time the subject could exert sufficient force by sustained contraction of the leg and hip muscles to hold the dynamometer indicator at a pre-determined figure. Leg endurance was measured in seconds.

PART I. PROCEDURE

The following measurements were secured upon each subject in this part of the study: leg strength, leg endurance, age, height, weight, total leg length, lower leg length and sitting height (*groups 2* and *3*). Subjects were fully dressed while leg strength and leg endurance were measured. For other measurements, subjects were clad only in shorts.

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Apparatus. A leg dynamometer was constructed for the purpose of measuring leg strength and leg endurance. The apparatus consisted of a salvaged B-24 seat-assembly equipped with a standard safety belt and salvaged B-24 rudder pedals mounted upon a low table. The seat was mounted upon the original seat tracks, making horizontal or vertical adjustment possible. It was found early in the study that the seat construction would not withstand the force to which the apparatus would be subjected. For this reason an angle iron brace was attached to the rear of the seat and then extended to the dynamometer table top. In order to accomplish the necessary movement, the pedals were mounted upon especially constructed pedal-tracks. A cable was attached to the rear of each pedal and secured to a standard spring dynamometer (2000-pound capacity). The pedals could be moved independently when force was exerted. Force exerted upon either pedal was measured in pounds.

Dynamometer Assembly for Measuring Leg Endurance. In this part of the study the subject was required to maintain a force of 300 ± 10 pounds to the limit of his endurance. Two lights mounted on the dynamometer housing and controlled by microswitches attached to the dynamometer served as visual indicators. A roller-arm attached to the dynamometer shaft activated a green light at 290 pounds and a red light at 310 pounds. The flashing of the green light was an indication that additional force was needed; the red light indicated that too much force was being exerted. The subject was instructed to hold the pedal so that neither light was activated.

During testing, the subject's hands were held upon a B-29 control wheel. There was free play in all movements of the wheel so that no assistance was afforded the subject.

Methods Used in Securing Measurements. Leg strength. As a result of counsel received from returned combat pilots of heavy bombers, the seat adjustment for each subject for measuring leg strength and leg endurance was such that when the foot was on the pedal, the angle at the knee was 111 ± 5° and at the ankle 60 ± 5°. Angles at the knee and ankle were measured with a goniometer. Tables for seat adjustment in reference to lower leg length were computed. Reference to these tables and the use of a horizontal scale on the table top and a vertical scale on the seat-post facilitated rapid seat adjustments. The same seat adjustment was used while the measurements for both leg strength and leg endurance were secured.

In securing the data for leg strength the first subject was measured for strength of right leg—this was followed by the measurement of the left leg. The second subject followed the reverse order. The third subject followed the order of the first, etc. Each subject was required to engage in three trials with each leg with one minute rest between trials alternating legs for each trial. The foot of the leg to be tested was placed upon the pedal while the other foot remained upon the floor board. The subject exerted as much force

as possible by the extension of the hip and leg after which the pressure was released. Strength was recorded to the nearest 10 pounds. This was a gradually developing tension until the subject had reached his maximum strength.

Total leg length. This measurement is defined as the total length of legs from soles of feet to the buttocks while the subject was in a sitting position with the backs of the legs pressed firmly against the table top. A narrow table 2 feet in height and 18 inches in width was constructed for measuring total leg length. This table was equipped with a backrest inclined backward at an angle of 30° and a sliding stop set at right angles to the table top. As the subject kept his hips firmly pressed against the backrest and inclined his body forward by grasping the side of the table top, the sliding stop was pressed firmly against his feet. Measurements were read from a scale on the table top.

Leg endurance. This measurement followed the leg strength measurement after the subject had rested for one minute. He began the leg-endurance test with the same leg with which he started the leg-strength test. The leg was extended sufficiently to register 300 pounds ± 10 on the dynamometer as indicated by the lights. After a rest period of 2 minutes the other leg was measured for endurance. A stop watch was used for recording the elapsed time. During strength testing, subjects were not informed as to the amount of force exerted nor were they informed as to the elapsed time during endurance testing. Subjects were not allowed to time themselves.

Height. The subject stood with his back to the stadiometer; heels together and centered; feet as nearly parallel as possible. The head and body were centered laterally with respect to the stadiometer. The head was held with 'chin in' so that a horizontal line could pass through the external auditory meatus and the external canthus of the eye. The subject took a deep breath and held it until the measuring slide was lowered until it was firmly in contact with the head. Recordings were made to the nearest tenth of an inch.

Sitting height. The subject sat on a bench 18 inches in height, hips, back, shoulder blades, and head in contact with the stadiometer; feet parallel with soles flat on the floor; lower legs at right angles to the thigh; forearms resting on the thighs. The remainder of the method was the same as for height.

Lower leg length. With the subject sitting upon a table with legs hanging over the edge, the distance from the center of the plantar surface of the heel to the horizontal surface of the knee was measured with a sliding-arm caliper. Measurements were recorded to the nearest tenth of an inch.

PART II. PROCEDURE

This part of the study was done for the purpose of determining whether additional experimentation would show a decrement in endurance time directly proportionate to increases in force requirements and whether other measure-

ments might be closely correlated with leg strength and leg endurance. The following test items were included: leg strength, leg endurance, height, weight, girth of thighs, girth of legs, and grip strength of right and left hands, lower leg length (used for seat adjustment).

It was found that there was no significant difference between each of the 3 trials with each leg for Part I. Therefore, during Part II only one trial with each leg (following an indoctrination trial with each leg) was used for this part of the study.

Leg Endurance—Apparatus. The dynamometer assembly was modified so that the amount of tension could be changed readily. The upper increment for measuring leg endurance was determined by the subject's leg strength. A movable masonite collar, containing contact points, was placed around the

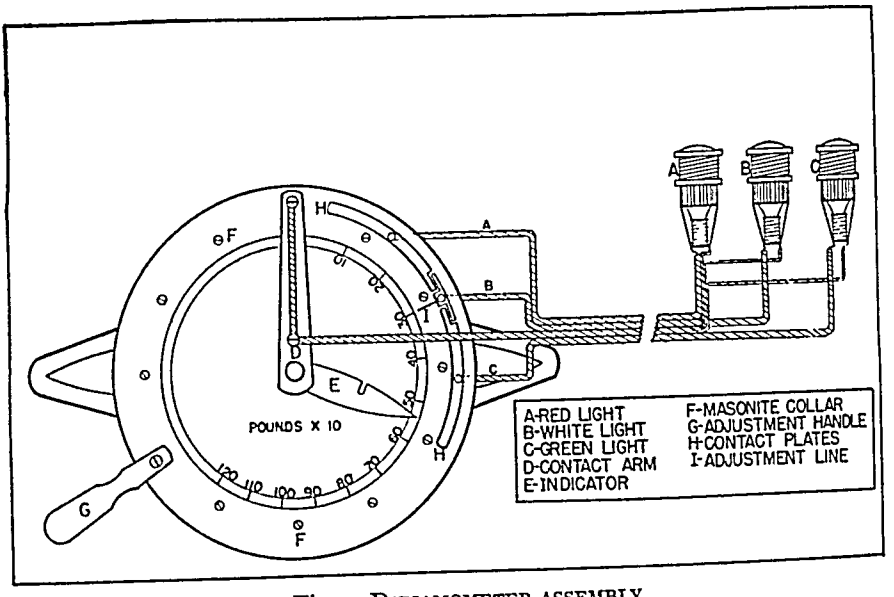

Fig. 1. DYNAMOMETER ASSEMBLY

outer edge of the dynamometer face (fig. 1). This arrangement made it possible to set the dynamometer at the desired point of resistance. A roller-arm was attached to the dynamometer shaft. When the roller attached to the arm came in contact with the metal points on the masonite collar, one of the 3 lights on the dynamometer housing was activated. A cumulative electrically operated timer which indicated the elapsed time in seconds and tenths was placed in the circuit with the white light. When the force for which the dynamometer was set (±10) was applied, the white light and timer were automatically activated. When force was relaxed to the extent of 10 pounds, the timer was inactivated and a red light indicated that additional force was necessary. When the force exerted was 10 pounds in excess of that for which the dynamometer was set, a green light was activated and the timer was inactivated. The green light was a signal that too much force was being exerted. For example, if the

subject showed a maximum strength of 560 pounds for the right leg and 610 pounds for his left, he was scheduled for endurance trials with the right leg on successive days with the dynamometer set at each of the following markings: 200, 300, 400, 500, and 600 pounds; and for the left leg at 200, 300, 400, 500, 600, and 700 pounds. The elapsed time was recorded by the investigator whenever the subject had completed his endurance trial.

In order to eliminate bias, which might have occurred by following a definite sequence of testing, a randomized order was followed in measuring leg endurance at the various increments.

Methods of Securing Other Measurements. For securing girth measurements, the Gulick spring tension anthropometric tape was used while the subject was in a standing position. The girth of the lower leg was taken at the point of greatest circumference. The girth of the thigh was taken at the line of the gluteal fold. Strength of grip was measured with a standard hand dynamometer. Each subject was allowed three trials with each hand alternately. One minute was allowed between trials. The mean grip strength for each hand was used in calculating the subsequent coefficients of correlation.

RESULTS

Coefficients of Reliability. Preliminary experimentation yielded the following results relative to coefficients of reliability for test items.

Total leg length. Six repeat measurements taken by each of 3 observers on each of 21 subjects yielded a coefficient of reliability of 0.99.

Height. Two determinations by each of two observers on 20 subjects gave a coefficient of reliability of 0.98.

Sitting height. Thirty subjects were measured 6 times each by the same observer. The coefficient of reliability was found to be 0.99.

Leg strength. A coefficient of reliability of 0.97 was first secured from the data obtained from 3 determinations for each leg upon 55 subjects. Following the collection of the data for Part I of the study, the coefficient of reliability for leg strength was computed from the data obtained from 515 subjects. For 6 determinations (3 for each leg) for the 3 groups of subjects involved, the coefficients of reliability varied from 0.96 to 0.93.

Leg endurance. Repeat determinations for 34 of 55 subjects available for retest showed a coefficient of reliability of 0.68 for both legs. From the data secured from one determination for each leg for the 3 groups involving 515 subjects the coefficient of reliability was found to vary from 0.837 to 0.863.

Means for the leg strength for the 4 groups are shown in table 1. The means for *groups 1, 2,* and *3* are based upon the average of 3 determinations with each leg and the means for *group 4* are based upon one determination for each leg. The means and standard deviations for leg endurance for *group 4* are shown in table 2. It will be noted that the mean for strength of the left leg for each

group is greater than that of the right leg. There is a tendency for the left leg to be significantly stronger than the right for *groups 1, 2,* and *3*. The mean strength of the right leg for *group 4* is not significantly greater than the strength of the left leg. Generally, there was no tendency for one leg to show greater

TABLE 1. MEANS AND STANDARD DEVIATIONS OF MEASUREMENTS ON ALL GROUPS

ACTIVITY	GROUP 1		GROUP 2		GROUP 3		GROUP 4		GRAND MEAN
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D	
Leg strength									
right	581		555		556		568		553
left	616[1]		581[1]		608[1]		584		578
average	599	97.0	568	95.0	582	105.0	576	93.0	565
Leg endurance									
right	130[2]		98[1]		149		114.6		123
left	127		89		139		107.7		113
average	129	68.9	93	54.5	144	84.5	111.1	61.3	118
Age, yrs.	20.7	2.4	23.6	1.8	22.5	2.8			21 7
Height, in.	69.8	2.4	69.7	2.5	69.6	2.4	70.0	2.0	69 8
Weight, lbs.	156.8	17.5	160.7	18.0	158.7	18.2	153.8	13.2	157 5
Total leg length, in.	41.1	1.8	41.1	1.9	40.6	1.8			40 9
Lower leg length, in.	21.5	1.0	21.1	1.1	21.1	1.0			21 3
Sitting height, in.			36.5	1.3	35.7	1.3			36 1
Thigh girth									
right							21.1	1 3	
left							20.9	1 2	
average							21.0		21 0
Leg girth									
right							14.4	.90	
left							14.2	.80	
average							14.3		14 3
Mean grip							123.2	13.6	123 2

[1] Significantly greater than for other leg at a .01 level of probability.

[2] Endurance taken for *groups 1, 2* and *3* with the dynamometer set at 300 lbs. only.

TABLE 2. MEANS AND STANDARD DEVIATIONS FOR LEG ENDURANCE WITH DYNAMOMETER SET AT VARIOUS INCREMENTS OF RESISTANCE

		Right Leg				
Resistance, lbs.	200	300	400	500	600	700
Mean	218.5	114.6	68.4	39.6	20.1	11.7
S.D.	122.8	62.9	31.7	21.2	12.8	7.8
		Left Leg				
Mean	188.0	107.7	70.3	40.6	20.8	14.6
S.D.	124.0	59.7	39.1	22.2	11.7	8 4

endurance than the other. However, in *group 2* the mean endurance for the right leg was significantly greater than that for the left leg. It will be noted that *group 1* (aviation students) showed the greatest mean strength (599 pounds) and aviation cadets (*group 3*) had the second highest mean strength

(582 pounds). In leg-endurance measurement, the cadets were far superior with a mean score of 144 seconds and the aviation students were second with a mean of 129 seconds. It has been suggested that these 2 groups showed superior performance because of the fact that each participated daily in 2-hour physical training periods. This was not the case with officers in *groups 2* and *4*. It should

TABLE 3. TABLE OF COEFFICIENTS OF CORRELATION FOR ALL GROUPS

	GROUP	ENDURANCE	AGE	HEIGHT	WEIGHT	TOTAL LEG LENGTH	LOWER LEG LENGTH	SITTING HEIGHT
Strength	*1*	+0.35[1]	−0.01	+0.21[1]	+0.57[1]	+0.12	+0.21[1]	
	2	+0.26[1]	+0.05	+0.17	+0.43[1]	+0.17	+0.22[1]	+0.17
	3	+0.32[1]	+0.15	+0.30[1]	+0.56[1]	+0.21[1]	+0.29[1]	+0.34[1]
	4	+0.40		+0.16	+0.64[1]			
Endurance	*1*		−0.05	+0.01	+0.15	+0.01	+0.04	
	2		−0.04	+0.15	+0.12	+0.07	+0.10	+0.14
	3		−0.09	+0.07	+0.10	+0.17	+0.02	+0.09
Age	*1*			−0.07	+0.04	−0.06	−0.08	
	2			+0.05	−0.01	+0.002	+0.02	−0.03
	3			−0.03	+0.18	−0.01	−0.04	+0.03
Height	*1*				+0.55[1]	+0.88[1]	+0.84[1]	
	2				+0.57[1]	+0.90[1]	+0.89[1]	+0.74[1]
	3				+0.57[1]	+0.88[1]	+0.84[1]	+0.74[1]
Weight	*1*					+0.49[1]	+0.55[1]	
	2					+0.61[1]	+0.58[1]	+0.51[1]
	3					+0.48[1]	+0.52[1]	+0.60[1]
Total leg length	*1*						+0.86[1]	
	2						+0.88[1]	+0.52[1]
	3						+0.85[1]	+0.45[1]
Lower leg length	*2*							+0.51[1]
	3							+0.48[1]

N *group 1* = 163. To be significant, r should exceed .20 *group 1*; N *group 2* = 175. To be significant, r should exceed .19 *group 2*; N *group 3* = 177. To be significant, r should exceed .19 *group 3*.

[1] Significant at .01 level of probability.

be mentioned, also, that the officers in *group 2*, having recently returned from combat, were somewhat lacking in enthusiasm.

In an attempt to determine the relationship between variables, Pearsonian coefficients of correlation were computed (tables 3 and 4).

For *groups 1, 2,* and *3* the coefficients of correlations between leg endurance and leg strength were found to be significant but low (+0.35, +0.26 and +0.32, respectively). However, the data for *group 4* show significant coefficients of correlation between leg strength and leg endurance for all units of dynamometer

resistance except 700 pounds for the right leg. For the left leg, significant coefficients of correlation were found with dynamometer resistance at 400, 500, and 600 pounds (table 4). While the coefficients of correlation between leg endurance and other variables used in *groups 1*, *2*, and *3* were not found to be significant, several of the variables used in *group 4* correlate significantly with leg endurance (table 4). However, the only degree of consistency in this regard is with the dynamometer set at 200 pounds. Weight, mean grip strength, calf girth and thigh girth correlate significantly with endurance for the right leg. For the left leg, the coefficient of correlation between leg endurance and leg strength is not significant.

Considering leg strength in relation to the other variables, the coefficients of correlation between weight and strength are significant and larger than other

TABLE 4. COEFFICIENTS OF CORRELATION BETWEEN WEIGHT, LEG STRENGTH, MEAN GRIP STRENGTH GIRTH OF THIGH AND GIRTH OF CALF VS. LEG ENDURANCE WITH RESISTANCE AT 200, 300, 400, 500, 600, AND 700 POUNDS FOR SUBJECTS IN GROUP 4

RESISTANCE, LB.	RIGHT LEG							LEFT LEG						
	Weight r	Mean grip r	Calf girth r	Thigh girth r	Leg strength r	$r_p = .01$	N	Weight	Mean grip r	Calf girth r	Thigh girth r	Leg strength r	$r_p = .01$	N
200	.54[1]	.35[1]	.39[1]	.33[1]	.36[1]	.30	75	.49[1]	.43[1]	.33[1]	.41[1]	.19	.30	75
300	.48[1]	.13	.33[1]	.21	.47[1]	.30	75	.28	.16	.23	.20	.23	.30	75
400	.29	.22	.24	.25	.31[1]	.30	74	.36[1]	.17	.23	.10	.31[1]	.30	75
500	.56[1]	.22	.48[1]	.27	.48[1]	.30	70	.54[1]	.29	.36[1]	.35[1]	.40[1]	.30	72
600	.34	.24	.33	.18	.41[1]	.35	51	.29	.24	.25	.16	.41[1]	.35	50
700	.07	.34	.14	.15	.45	.59	18	.01	.28	.21	.04	.56	.59	16
Leg strength	.64[1]	.31[1]	.53[1]	.48[1]		.30	75	.63[1]	.33[1]	.54[1]	.30[1]		.30	75

All coefficients of correlation were found to be positive.

[1] Significant on a .01 level of probability.

coefficients for this variable with data for *group 4* showing a creditable correlation (+0.64 right leg, +0.63 left leg). The data for *groups 1*, *2*, and *3* show coefficients of correlation between weight and strength of +0.57, +0.43, and +0.56, respectively.

For *group 4*, the data showed significant coefficients of correlation between leg endurance and weight with resistance of 200, 300, and 500 pounds for the right leg and 200, 400, and 500 pounds for the left leg. Considering both legs, the highest coefficients of correlation between these two variables were found at 500 pounds (+0.56 and +0.54).

Referring to table 1 and figure 2 it will be noted that, as would be expected, based upon the standard deviations, the endurance becomes less variable as the resistance is increased. The endurance time for the right leg decreased at

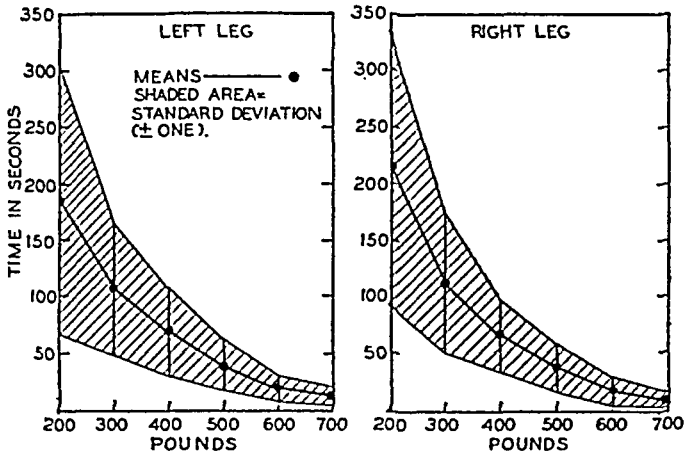

Fig. 2. LEG ENDURANCE CURVES

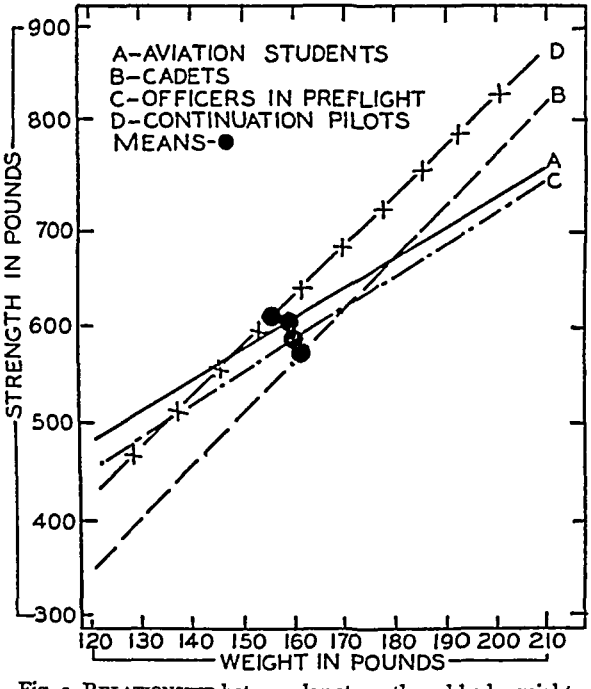

Fig. 3. RELATIONSHIP between leg strength and body weight

an average of 43.4 seconds for each 100 pounds of resistance. The reduction in endurance time for the left leg was on the average of 34.7 seconds for each 100 pounds of increase in resistance.

The data for strength of grip (*group 4*) when compared with leg endurance showed significant but low coefficients of correlation for each leg with a 200-

pound resistance. Low but significant coefficients of correlation were found between the mean grip strength and leg strength for each leg (+0.31 and +0.33).

From the data secured from the subjects in *group 4* the coefficients of correlation between strength for each leg and mean grip, calf girth and thigh girth were found to be significant. In experienced pilots the girth of calf would seem to be a good index of leg strength since the coefficients of correlation between these two variables were found to be +.53 for the right leg and +.54 for the left. However, the coefficients of correlation between leg strength and weight for each group (table 3 and 4) would indicate that weight is the best index of leg strength. For this reason regression formulas, showing the mean leg strength increases per pound of body weight for each group, were computed as follows: *group 1*, 1.895 pounds; *group 2*, 3.161 pounds; *group 3*, 1.941 pounds; and *group 4*, 4.515 pounds. Regression lines for all groups are shown in figure 3.

SUMMARY AND CONCLUSIONS

Five hundred ninety potential pilots and pilots grouped in the following categories were used as subjects: *group 1*, 163 aviation students; *group 2*, 175 combat officer returnees undergoing preflight training; *group 3*, 177 aviation cadets; *group 4*, 75 pilots undergoing continuation training.

Especially designed apparatus was used for securing data relative to leg strength and leg endurance. In addition to these measures, data relative to the following were secured on all subjects: height, weight, age and lower leg length. In addition, total leg length measurements were taken on all subjects in *groups 1* and *2*; and sitting height for *groups 2* and *3*. The girth of the thigh, girth of the leg and grip strength were measured for the subjects in *group 4*.

The analysis of the data revealed the following: Coefficients of correlation between leg endurance and age, height, weight, total leg length and sitting height in the data secured by measuring the potential pilots contained in *groups 1*, *2* and *3* were not found to be significant. Low but significant coefficients of correlation were found between leg endurance and leg strength for these groups.

Considering the measurements for each leg as to significance, there was little consistency in the coefficients of correlation between leg strength and leg endurance. Data for the right leg for the group of pilots gave significant coefficients of correlation between leg strength and leg endurance at all increments except with the dynamometer set at 700 pounds. Significant coefficients of correlation between leg strength and leg endurance were found for the left leg only with the dynamometer set at 400, 500 and 600 pounds.

In addition to the significant coefficients of correlation between leg strength and leg endurance, some significant coefficients of correlation were found between the other variables and leg endurance (table 4). However, the only consistency in this regard was shown in the data from the group of pilots which

showed significant coefficients of correlation between leg endurance with the dynamometer set at 200 pounds and mean grip strength, thigh girth and calf girth.

Endurance time for the right leg decreased at an average of 43.4 seconds for each 100 pound increase in resistance; and an average of 34.7 seconds for each 100 pound increase resistance for the left leg. The mean endurance time for all subjects (dynamometer set at 300 pounds resistance) was 118 seconds. The group of aviation cadets was less variable than the other groups. The coefficients of correlation between weight and leg endurance do not follow a definite trend. However, the coefficients of correlation between these two variables with the dynamometer set at 500 pounds were found to be substantially significant. There is a significant relationship between body weight and leg strength. This is more pronounced for the pilot than for the potential pilot. Coefficients of correlation between the girth of the leg and leg strength were substantially significant but perhaps too low to use for prediction purposes.

The data secured from the groups containing potential pilots showed the mean strength for the left leg to be significantly greater than that for the right leg. The data secured from measuring the pilots showed a greater mean strength for the left leg but the difference was not significantly greater than the mean for the right leg. The mean leg strength for all subjects was found to be 552 pounds for the right leg and 578 pounds for the left leg. The data for pilots with a standard deviation of 93 were less variable than other groups. The highest mean for both right and left legs was 599 pounds for the group of aviation students.

The height of the individual is not related to leg strength nor leg endurance. Since there is a significant relationship between body weight and leg strength, the reduction in weight would materially reduce leg strength. However, the reduction of weight would not materially reduce leg endurance.

The kind assistance of Dr. P. V. Karpovich, Raymond Weiss, R. R. Rankin and Stanley Nicijewski is gratefully acknowledged.

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In addition to the significant coefficients of correlation between leg strength and leg endurance, some significant coefficients of correlation were found between the other variables and leg endurance (table 4). However, the only consistency in this regard was shown in the data from the group of pilots which

served at −8°C. (room temperature of 26°C.); the ingestion time was again 5 minutes.

In the experiments on gastric motility roentgenograms were taken at 5, 30, 60, 90, 120 and 210 minutes after the test meal had been eaten. The subjects remained seated in the air-conditioned room between roentgenograms. The gastric shadows were traced onto transparent paper from the developed roentgenograms and the areas of the shadows were measured with a planimeter; all gastric areas were expressed as percentages of the area in the 5-minute roentgenogram (see ref. 5, for further details of the procedure). Blood was drawn from an antecubital vein with a minimum of stasis immediately following each roentgenogram for blood glucose concentration determinations by the Nelson (6) photometric adaptation of the Somogyi method.

Skin temperatures were recorded from small iron-constantan thermocouples by a Leeds and Northrup 'Speedomax' recording potentiometer. The thermocouples were fastened firmly against the skin with scotch tape. In the first experiments the thermocouples were placed on the forehead, chest, finger and toe but because of the lack of temperature changes on the forehead and chest and the rather small or irregular changes in the toe, in most cases only finger skin temperatures were recorded. Rectal temperature was recorded by an indwelling thermocouple. A thermocouple placed near the subject recorded the room air temperature.

The standard three electrocardiographic limb leads were taken in the experiments involving test meals of different temperatures. Blood pressure was measured by auscultation of the brachial artery using a standard blood pressure cuff and anaeroid gauge. Pulse rates were counted by palpation of the radial artery. In the cold pressor test blood pressure and pulse rates were measured before, at 15 to 30 seconds and at 45 to 60 seconds after submerging the hand in ice water to the wrist.

RESULTS

Gastric Motility and Meal Temperature. The relation between the temperature of the test meal and gastric motility is presented in figure 1. Statistical analyses revealed no significant differences in the rate of evacuation of the test meals from the stomach that were related to the temperature of the test meal. The largest differences which were between the 26°C. and the 65°C. meals would, according to the F-test, be expected to occur by chance in about 1 in 10 cases. However, as shown in figure 1, there was a slight difference in the mean rate at which the 3 test meals were emptied from the stomach; the meal served at 26°C. emptied fastest, the hot meal slowest and the cold meal occupied an intermediate position. These small differences occurred early in the emptying process; after 60 minutes the 3 curves were essentially parallel.

Blood Sugar Concentration and Meal Temperature. In figure 2 are presented

the data for the blood sugar response to the test meal at the different temperatures. An average increase in blood sugar concentration of from 10 to 20 mg/100 cc. of blood occurred in all cases. The response was rapid with the maximum

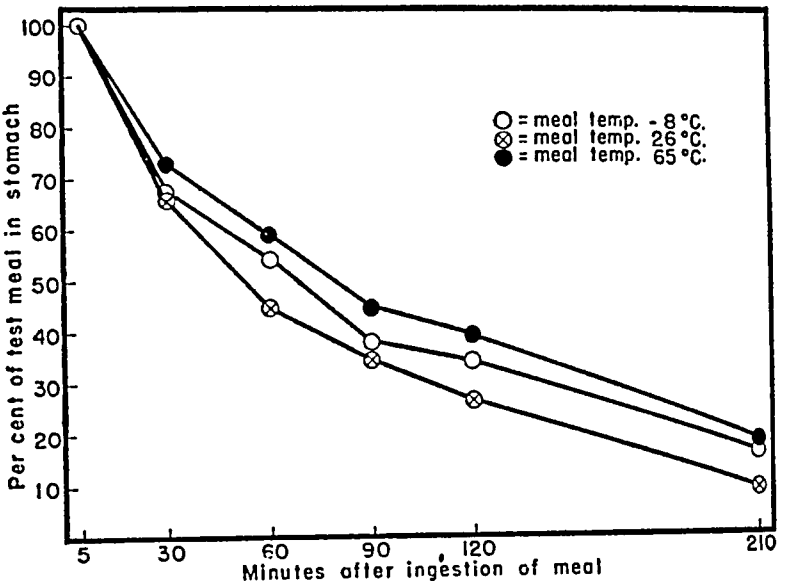

Fig. 1. RELATION OF GASTRIC MOTILITY and temperature of the gastric meal. All values are expressed as percentage of area of gastric shadow immediately after test meal was eaten.

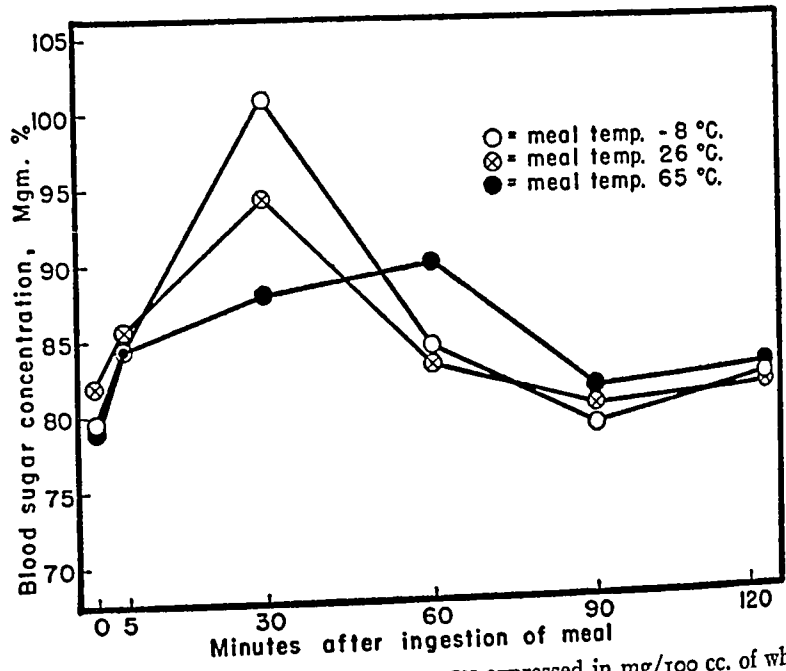

Fig. 2. RELATION OF BLOOD SUGAR CONCENTRATION expressed in mg/100 cc. of whole blood and temperature of thermal stimulus.

increase reached at 30 minutes for the cold and warm test meals and at 60 minutes for the hot meal.

The magnitude of the blood sugar concentration increase was related to

the temperature of the test meal. The greatest response (20 mg/100 cc. of blood) occurred when the test meal was served frozen and the least response (10 mg/100 cc. of blood) occurred after the hot test meal. The difference between the hot and cold test meal blood sugar response at 30 minutes was statistically significant ($F = 7.00$, F for $5\% = 6.60$). The blood sugar response to the warm test meal was mid-way between the hot and cold test meal but statistically was not significantly different from either.

Skin Temperature and Meal Temperature. The relation between finger skin temperature and test meal temperature is presented in figure 3. Both meal temperature and room temperature were varied. The finger skin temperature did not differ significantly from the pre-ingestion control value when the test

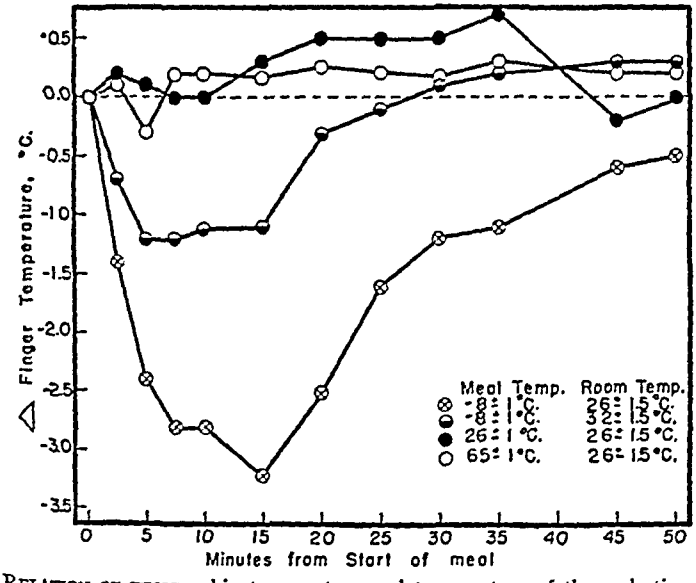

Fig. 3. Relation of finger skin temperature and temperature of thermal stimulus and room temperature. Skin temperatures are given as °C. change from the pre-stimulation values.

meal temperature was either warm or hot and the room temperature was either 26°C. or 32°C. (data not included in fig. 3).

The finger skin temperature response to the ingestion of the cold test meal was rapid at room temperatures of both 26°C. and 32°C.; the response being greater at the lower room temperature. When the room temperature was 26°C. the maximum depression of finger skin temperature of 3.25°C. occurred 15 minutes after the beginning of ingestion of the test meal. After the first 15 minutes the skin temperature increased but was still about 0.5°C. below the control value at 50 minutes. The skin temperature response was much less pronounced when the room temperature was 32°C.; a decrease of 1.25°C. occurred during the ingestion of the cold test meal (5 minutes). In the next 10

minutes little change occurred but by 25 minutes the skin temperature was again normal.

Blood Pressure and Pulse Rate and Thermal Stimulus Size. The blood pressure and pulse rate response to cold test meals of different sizes was tested by comparing the response to a 400-gram and a 100-gram portion of ice cream served at −8°C. with room temperature at 26°C. The data are given in table 1.

An average systolic blood pressure rise of 13.4 mm. Hg occurred within the first minute of ingestion of the 400-gram test meal. The increase reached a maximum of 14.8 mm. Hg at the finish of the meal and then rapidly returned to the control level. The diastolic pressure response was approximately the same as the systolic response (constant pulse pressure) with a maximum increase of 17.6 mm. Hg at 2 minutes from the start of ingestion and 17.4 at the end of the

TABLE 1. RELATION OF SIZE OF COLD MEAL (400- OR 100-GM. ICE CREAM) TO CHANGES IN SYSTOLIC AND DIASTOLIC BLOOD PRESSURE IN MM. Hg AND PULSE RATE IN BEATS PER MINUTE

MEAL SIZE	TIME	SYSTOLIC B.P.			DIASTOLIC B.P.			PULSE RATE		
		Absol.	Diff.	S.D.Δ	Absol.	Diff.	S.D.Δ	Absol.	Diff.	S.D.Δ
gm.		*mm. Hg*			*mm. Hg*					
400	Control	125.0			74.6			64.6		
	1 min.	138.4	13.4	4.6	89.4	14.8	6.7	83.4	18.8	7.5
	2 min.	139.0	14.0	6.0	92.2	17.6	6.8	84.8	20.2	8.2
	5 min.	139.8	14.8	4.5	92.0	17.4	6.1	81.4	16.8	9.4
	7 min.	128.0	3.0	2.9	79.4	4.8	5.4	66.8	2.2	7.5
100	Control	123.3			72.9			66.0		
	1 min.	124.4	1.1	3.0	75.1	0.5	5.9	73.5	8.9	4.7
	2 min.	124.6	−1.3	3.9	77.6	4.7	6.2	71.3	5.3	6.0
	5 min.	126.4	3.1	5.0	77.6	4.7	6.5	68.7	2.7	6.0
	7 min.	125.3	2.0	5.5	75.1	2.2	4.9	66.9	0.9	6.0

Absol. = absolute values; diff. = change from control value; S.D.Δ = standard deviation of the differences. Room temperature was 26° C. and meal temperature − 8° C.

meal; the diastolic pressure was also substantially normal soon after the meal was finished. The blood pressure did not change significantly when the 100-gram test meal was ingested.

The pulse rate increased approximately 30 per cent during the ingestion of the cold 400-gram test meal. The response was rapid, reaching a plateau during the first minute and remaining at the high level during the ingestion period. Within 2 minutes after the finish of the meal the pulse rate was again normal. The 100-gram test meal was accompanied by an early pulse rate increase of about 15 per cent during the first minute. The response was, however, only transient and the pulse rate was back to normal by the end of the ingestion period.

Skin Temperature and Thermal Stimulus Size. The relation of skin temperature changes to the size of the cold test meal is presented in figure 4. The finger

skin temperature (average of left and right hand) decreased slightly during the first minute of ingestion of the 400-gram meal. As more of the meal was eaten the finger skin temperature progressively declined, dropping 1.1°C. during the 5 minutes of ingestion. The skin temperatures continued to decline during the 10 minutes that records were taken following ingestion of the meal; a decrease of 2.5 and 2.7°C. occurred in the finger of the right and left hand, respectively. When the 100-gram test meal was given there was only a slight decrease in the finger skin temperature.

Internal Versus External Thermal Stimulation. A comparison was made of the systolic blood pressure response to the ingestion of 400 grams of ice cream at −8°C. with the response to the immersion of one hand in ice water for one minute. The *internal* application of the cold resulted in an average rise in systolic blood pressure of 14.8 mm. Hg with a range of 12 to 32 mm. Hg. The mean systolic blood pressure response to the *external* application of cold was a 16.2 mm. Hg with a range of 5 to 37 mm. Hg. A systolic blood pressure increase of

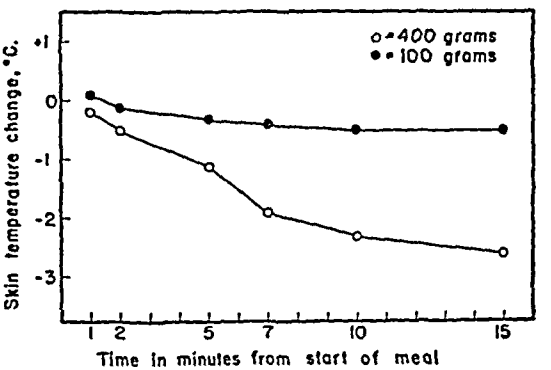

Fig. 4. Relation of size of cold test meal and changes in finger skin temperature. Room temperature was 26° C. and meal temperature, −8° C.

20 mm. Hg or more was recorded for 2 subjects on internal and 3 on external cold stimulation. None of the subjects responded with an increase in systolic pressure of 20 mm. Hg or more on *both* tests.

DISCUSSION

The lack of general agreement in the literature on the relation of test meal temperature and gastric motility is not surprising in view of the differences in experimental procedures and test meal composition used by the investigators. Hepburn (7) observed an increased gastric emptying time of 15 minutes in 4 experiments, 30 minutes in 4 and no increase in one when iced water was given with an Ewald meal. Eberhard (4) reported a delay of 30 to 45 minutes in gastric emptying time when 90 grams of ice cream or 250 cc. of iced water was given at the end of a full meal. Gershon-Cohen (8) on the other hand, found that a cold barium sulphate—Liebig's extract mixture—began to leave the stomach immediately on ingestion and was rushed through the jejunum and ilium while

the hot mixture was slow to leave the stomach. In both cases gastric activity had returned to normal in 30 minutes. None of the authors subjected their data to critical statistical analysis.

Because of the large inter- and intra-individual variation in gastric emptying time, the statistical significance of the changes reportedly due to the test meal temperature is questionable. In the present experiment where the same group of trained subjects was used throughout no statistically significant relationship was found between gastric emptying time and the temperature of the test meal.

The increase in the blood sugar concentration following the test meals could not have been due to the absorption of the sugar in the test meal. Little if any of the sucrose could have been hydrolyzed and absorbed in 5 minutes after the ingestion of the test meal; during that period there was a definite increase in the blood sugar concentration. At 30 minutes when the blood sugar concentration had reached its maximum only 30 per cent of the test meal had been evacuated from the stomach. The rapidity of the blood sugar response and the influence of the temperature of the test meal on the magnitude of the response suggest reflex and/or hormonal factors initiated by the ingestion of food and augmented by the temperature of the food as the basic mechanisms involved. This concept is supported by the observations that the blood sugar concentration was increased following the introduction of cold water into the stomach of cats (9) and dogs (10, 11).

Peripheral vasoconstriction and a decrease in skin temperature as a response to the ingestion of cold foods would be anticipated from the general observation that a sensation of cooling frequently occurs when ice cream is eaten. It has been demonstrated that a variety of other factors (drugs, emotions, hot and cold applications, smoking) produce changes in skin temperature (12–17). The 3.5°C. drop in finger skin temperature following the cold test meal was large even though localized in character. It is not surprising that the major change in skin temperature occurred in the finger since it has been demonstrated that the fingers and toes have a much larger vasomotor response to the demands of heat regulation than other skin areas (16).

As is the case in most stimulus-response reactions, the size of the thermal stimulus, in this case the amount of the ice cream eaten in a constant time, determined the extent of the response of the finger skin temperature, systolic and diastolic blood pressure and pulse rate. With the 400-gram stimulus the blood pressure and pulse rate rise was prompt but lasted only while the ice cream was being eaten. This suggests that the response is a reflex initiated by stimulation of the cold and pain receptors in the mouth by the cold test meal.

The skin temperature response was slow and progressive as compared to the rapid blood pressure and pulse rate response. Some lag between vasocon-

striction and change in skin temperature would be expected but hardly 15 minutes if the vasoconstriction in the skin occurred at the same time that the blood pressure and pulse rate increased. It is apparent that the mechanisms involved in the blood pressure pulse rate response and the skin temperature response are not the same. The slowness of the skin temperature response suggests a hormonal mechanism. An increased adrenalin secretion as a result of local external cold applications has been reported in the cat (18).

The three standard electrocardiographic limb leads were taken before, during and after the ingestion of the test meals. The cycle length showed a significant increase to all the test meals. There was a small and variable depression of T_3 which was not related to the temperature of the meal but was similar to the changes reported after other types of test meals (19). No changes specifically related to the temperature of the meals were observed.

SUMMARY

The gastric motility, blood sugar concentration, blood pressure, pulse rate, electrocardiogram and skin temperature responses to internal thermal stimulation were measured in normal young men.

Gastric motility was not greatly altered by the temperature of the test meal when served. Blood sugar concentration was slightly and promptly increased after a test meal regardless of the temperature but the response was significantly greater when the test meal was served cold. Finger skin temperature dropped as much as 3.5°C. when a cold test meal was ingested. The response was prolonged and did not return to normal within 50 minutes.

Blood pressure increases of 15 to 20 mm. Hg were produced during the time the 400-gram cold meal was eaten; no increase occurred with the 100-gram meal. Pulse rate was increased 18 to 20 beats per minute during the ingestion of the 400-gram cold meal. With the 100-gram cold test meal the maximal pulse rate increase was less than half as great and the response was over by the time the meal had been ingested. The average systolic blood pressure response to the 400-gram cold test meal was about the same as that produced by immersion of the hand in ice water for 1 minute.

None of the test meals produced significant electrocardiographic responses except for the cycle length.

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Gusto-Olfactory Thresholds in Relation to Appetite and Hunger Sensations

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IT HAS OFTEN been suggested that appetite is somehow related to the sense of taste and smell. Recently, Goetzel (1) has claimed that appetite varies directly with acuity of the olfactory sense, and may be measured in terms of variation in olfactory thresholds.

Appetite may be defined simply as the desire to eat. Under normal circumstances deprivation of food in man gives rise to the desire to eat and to a complex constellation of sensations which include gastric and extragastric components. These we have called *hunger sensations* (2).

The present series of experiments were undertaken to study *1*) the relationship between appetite, accompanying hunger sensations and variations in the acuity of the senses of taste and smell, and *2*) the effect of an appetite-depressing drug on the thresholds of these senses and on hunger sensations.

METHODS

Acuity of the gusto-olfactory senses was measured by means of the thresholds for such simple and easily recognizable odors and tastes as might be encountered in ordinary eating, at intervals when appetite was marked, and following the ingestion of food. The noon-day meal was most convenient for this purpose.

Thresholds for the recognition of the substance, rather than for the perception of odor or taste, as such, were determined. This latter threshold (awareness of stimulation) was discarded as not being useful in ordinary eating behavior.

The subjects employed were medical and graduate students at this University, whose appetite patterns and hunger sensations were known from previous studies. The threshold for salt (sodium chloride) and sugar (sucrose) tastes and the smell of coffee were determined at 10:30 A.M., just prior to the noon meal, and at 2:00 P.M. ($1\frac{1}{2}$–2 hours after the ingestion of lunch).

Thresholds for taste were determined by the 'choice method' of Richter

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and MacLean (3), in which subjects are presented with two small glasses, one filled with distilled water and the other with varying concentrations of the substance tested. The subjects were instructed to sample the fluid in each glass as often as they desired until they were certain that they did or did not have the same taste. If the tastes were different they were instructed to name the taste perceived. The varying concentrations of each substance were randomized, and the subjects were ignorant of the order.

The solutions of sodium chloride employed ranged from 0.01 to 0.2 per cent in these steps: 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08. 0.09, 0.1,

TABLE 1. THRESHOLDS FOR SENSE OF SMELL AT VARIOUS TIMES OF DAY
(*Expressed as cc. of odorous air*)

SUBJECT	10:30 A.M.	BEFORE LUNCH, 12 NOON	AFTER LUNCH, 2 P.M.	SUBJECT	10:30 A.M.	BEFORE LUNCH, 12 NOON	AFTER LUNCH, 2 P.M.
P.S.	6.0/ 6.2	6.5/ 6.0	4.0/ 4.5	*F.A.*	9.0/8.5	9.5/9.5	9.0/8.5
D.M.	7.0/ 6.5	6.5/ 6.0	2.5/ 3.0	*D.K.*	4.5/5.0	6.0/6.0	6.5/6.0
	8.0/ 8.0	6.5/ 6.5	6.0/ 6.0		5.5/5.5	7.0/7.0	6.0/6.0
	8.0/ 9.0	8.0/ 8.0	5.0/ 5.5				
				A.L.	4.0/4.0	4.0/4.0	3.0/3.0
D.F.	7.1/ 7.5	7.0/ 7.5	7.0/ 9.5				
	10.0/11.0	9.0/11.0	10.0/10.0	*P.S.B.*	9.0/8.5	9.0/8.5	8.0/8.0
F.A.	9.0/ 9.5	6.5/ 9.0	6.5/ 7.5	*J.B.*	3.5/3.5	3.0/3.0	3.0/3.5
D.B.	4.0/ 3.0	3.0/ 3.0	4.0/ 4.0	*H.R.*	6.5/6.0	6.5/6.5	6.5/6.5
	4.5/ 4.5	5.0/ 4.5	4.0/ 4.5				
	2.5/ 3.0	4.0/ 3.5	4.0/ 4.5	*K.K.*	8.5/8.0	9.0/9.5	8.0/8.0
R.S.	7.0/ 7.5	8.0/ 7.5	8.0/ 8.5	*A.K.*	9.0/8.5	8.5/9.0	9.1/9.0
	7.0/ 7.5	7.0/ 7.0	4.5/ 5.5				
	5.5/ 5.0	5.5/ 5.0	5.5/ 5.5	*C.E.R.*	6.0/6.5	4.5/5.0	5.0/5.0
H.J.	13.0/13.5	14.0/14.0	13.0/13.0	*H.M.R.*	4.5/4.0	4.5/5.5	4.5/5.0
	10.0/10.0	11.0/11.0	7.5/ 8.0				
	6.0/ 6.0	5.5/ 6.0	5.5/ 6.0	Mean.....	6.92	6.95	6.35

and 0.2 per cent. The solutions of sucrose employed ranged from 0.1 to 1 per cent in steps of 0.1 per cent. Only one substance was tested for each subject on any one day.

Thresholds for smell (coffee) were tested by the method of Elsberg and Levy (4), in which a measured volume of odorous air is introduced in a single blast into the nostrils of the subject. The tests of any given volume were made at one-minute intervals to avoid fatigue. The threshold was the smallest volume of air which the subject immediately recognized in 2 out of 3 consecutive trials. The threshold was retested after a 10-minute interval during each test period.

In another series of tests, the effect of appetite-depressing doses of D-amphetamine was determined by giving each subject 10 mg. of this drug one hour before the noon meal on alternate days and retesting for thresholds.

RESULTS

Nine subjects were tested for their threshold for salt, 10 for the taste of sugar and 19 for the smell of coffee. All subjects had marked appetite (desire

TABLE 2. THRESHOLDS FOR SALT TASTE AND FOR SUGAR TASTE AT VARIOUS TIMES OF DAY
(*Expressed as percentage concentration o solution*)

SUBJECT	10:30 A.M.	BEFORE LUNCH, 12:00 NOON	AFTER LUNCH, 2:00 P.M.
	Thresholds for Salt Taste		
	%	%	%
D.B.	0.05	0.05	0.05
A.L.	0.05	0.05	0.04
H.R.	0.10	0.10	0.09
M.K.	0.07	0.08	0.07
D.K.	0.07	0.08	0.08
H.J.	0.07	0.06	0.07
J.C.	0.04	0.04	0.04
C.C.	0.07	0.07	0.07
E.K.	0.08	0.08	0.07
Mean.....	0.065	0.068	0.064
	Thresholds for Sugar Taste		
	%	%	%
D.B.	0.6	0.6	0.6
A.L.	0.6	0.6	0.5
G.A.	0.5	0.5	0.5
H.J.	0.3	0.3	0.3
K.S.	0.3	0.3	0.3
E.K.	0.7	0.7	0.8
H.R.	0.6	0.6	0.5
M.K.	0.6	0.6	0.6
D.K.	0.5	0.5	0.4
J.C.	0.4	0.4	0.3
Mean.....	0.51	0.51	0.48

o eat) and well developed hunger sensations when tested before the noon meal. ll noted the abolition of these sensations after eating. The results are summarized in tables 1 and 2.

It will be seen that there was rather marked constancy in each subject in he threshold for salt and sugar throughout the period tested, both during the evelopment of appetite and hunger sensations and following their subsidence.

The results of the olfactory threshold tests reveal a high degree of re-

producibility for the threshold at any one test period. The test-retest correlation coefficient was +0.98. There was, however, more variation in this threshold from period to period than for the gustatory thresholds. However, in neither the taste nor the olfactory thresholds are the differences between periods statistically significant.

Compared to the midmorning threshold, the olfactory thresholds at noon were unchanged in 22 tests, rose in 3 and fell in 3. Compared to the prelunch thresholds, those after eating were unchanged in 21 instances, rose in 1, fell in 6.

The results of the effects of 10 mg. of D-amphetamine are summarized in table 3. Six tests were performed in 6 subjects for salt thresholds, 7 tests in 7 subjects for sugar, and 8 tests in as many subjects for smell. In all instances the dose of D-amphetamine employed abolished all hunger sensations and markedly depressed the desire to eat. In 13 tests, there was no change in the

TABLE 3. THRESHOLDS FOR SENSE OF TASTE FOR SALT AND SUGAR AND FOR SENSE OF SMELL BEFORE AND AFTER D-AMPHETAMINE

(*Means and their respective standard errors*)

NO. OF SUBJECTS	TIME		
	10:30 a.m.	11:00 a.m.	Noon (before lunch)
	Salt taste threshold (% NaCl solution)		
6	0.061 ± 0.0098	10 mg. D-amphetamine orally	0.060 ± 0.0093
	Sugar taste threshold (% sucrose solution)		
7	0.51 ± 0.059	10 mg. D-amphetamine orally	0.48 ± 0.040
	Threshold for smell (cc. of odorous air)		
8	5.44 ± 0.57	10 mg. D-amphetamine orally	5.46 ± 0.58

sense of taste, one threshold for salt fell 0.01 per cent, one for sugar rose 0.1 per cent. In 8 tests of olfactory acuity the threshold rose in 4 cases, fell in 3, and was unchanged in one.

DISCUSSION

Changes in reflex excitability of the central nervous system associated with the periodic gastric hunger contractions have been demonstrated by Carlson (5) for the knee jerk. Thus, changes in threshold for the special senses of smell and taste associated with hunger sensations and appetite could not be ruled out a priori. However, we have failed to demonstrate constant changes for the acuity of taste, and have also failed to confirm the previous report on changes in olfactory acuity.

The present study indicates that minor variations in the acuity of the gusto-olfactory senses do occur, but these variations bear no constant relationship to the presence of appetite and the accompanying hunger sensations.

A dose of D-amphetamine which abolished the desire to eat had no consistent effects on these senses, in contrast to reported previous findings (1).

TABLE 4. ANALYSIS OF VARIANCE OF DATA ON TASTE AND OLFACTORY THRESHOLDS

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUM OF SQUARES	MEAN SQUARES
Thresholds for sense of smell at various hours of the day (see table 1)			
Between hours	2	5.9865	2.9932
Between individuals	25	422.8566	16.9142
Error	50	37.3269	0.7465
Total	77	466.17	
Thresholds for salt taste at various hours of the day (see table 2)			
Between hours	2	0.000051	25×10^{-6}
Between individuals	8	0.007626	953×10^{-6}
Error	16	0.000352	22×10^{-6}
Total	26	0.008029	
Thresholds for sugar taste at various hours of the day (see table 2)			
Between hours	2	0.0060	30×10^{-4}
Between individuals	9	0.5466	607×10^{-4}
Error	18	0.0274	15×10^{-4}
Total	29	0.5800	
Salt taste before and after D-amphetamine (see table 3)			
Treatment	1	0.000008	8×10^{-6}
Between individuals	5	0.005442	1088×10^{-6}
Error	5	0.000050	10×10^{-6}
Total	11	0.005500	
Sugar taste before and after D-amphetamine (see table 3)			
Treatment	1	0.0028	28×10^{-4}
Between individuals	6	0.2000	333×10^{-4}
Error	6	0.0172	29×10^{-4}
Total	13	0.2200	
Threshold for smell before and after D-amphetamine (see table 3)			
Treatment	1	0.0025	0.0025
Between individuals	7	35.2500	5.0357
Error	7	1.8875	0.2696
Total	15	37.1400	

We would stress the observation that suppression of appetite was accompanied by a parallel suppression of hunger sensations.

In table 4 an analysis of variance for each set of data is presented. In every instance it will be noted that the variance attributable to differences between hours of the day or to treatment with D-amphetamine is very small, in most instances smaller than the variances attributable to random sampling error. In no case is the F ratio (6) of these two mean squares significant. On the other hand, the variance assignable to differences between individuals is in all cases very large and the F ratio of this mean square to the mean square for error is highly significant. This indicates that almost all of the variation encountered was due to differences between individuals and that any one individual showed a very strong tendency to remain constant over a period of hours or after treatment with D-amphetamine. The important conclusion that can be drawn from these facts is that the reliability or reproducibility of the methods of measurement was excellent so that the failure to detect differences at various hours of the day or after treatment with D-amphetamine cannot be due to a masking of such differences by wide fluctuations due either to lack of reproducibility or to spontaneous random changes.

It may also be pointed out that these results are consistent with the clinical observation that complete anosmia has little effect on appetite, although olfaction may, under some circumstances, be important in the genesis of nausea and anorexia.

SUMMARY AND CONCLUSION

Only minor variations in the acuity of the senses of taste and olfaction were found to occur during the day. These bore no consistent relation to the presence or absence of hunger sensations and appetite (the desire to eat). The abolition of appetite by D-amphetamine is paralleled by suppression of the accompanying hunger sensations, but is not related to any consistent change in the acuity of the gusto-olfactory senses.

The various tests gave excellently reproducible results so that the failure to detect changes cannot be attributed to technical unreliability or to masking by random fluctuations.

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Effects of Bed Rest on Cardiovascular Function and Work Performance[1]

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IN RECENT YEARS there has been an intensification of interest in the problems of convalescence. It has been recognized that the speed with which a patient can be returned to a gainful occupation is influenced, in addition to the characteristics of the specific disease itself, by certain general conditions. Among those factors which are common to most disease states and which may be altered by management are the psychological attitude of the patient, the malnutrition which results from poor appetite and the effects of bed rest. The relation between the nutritional state and the course of disease has been extensively studied (1–4). The effects of bed rest in the treatment of disease has been discussed (5, 6) and evidence has been presented to support the practice of early rising after operation (7). In addition, it has been shown that a program of graded exercise in convalescence is useful in returning men to active duty earlier than would otherwise be the case (8).

The problem of the effects of bed rest per se has not received a great deal of attention. There is agreement on the effects of bed rest on nitrogen and mineral metabolism (9–12). There remain, however, general questions concerning the nature of deconditioning produced by bed rest, questions which are basic to the intelligent planning of a reconditioning program during convalescence. To what extent are the several fundamental components of fitness—coordination, speed, strength and endurance—affected by bed rest? How rapidly do the several items return to normal during the recovery period? It is

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the purpose of this paper to provide evidence on these points. Preliminary notes on this work have been presented elsewhere (12–14), and the effect of bed rest on the volume of the blood has been reported separately (15).

SUBJECTS

The 6 young men who acted as subjects in this study were volunteers recruited from Civilian Public Service Camps for conscientious objectors. These men were from 20 to 32 years of age. They were within ±10 per cent of the norm when compared to standard height-weight tables. One man (*A. W.*) had been a successful football player in college, but otherwise none had been physically either very active or very sedentary. Careful physical examination failed to reveal any noteworthy physical defects.

CONDITIONS

The men resided in the laboratory during the entire experimental period. During the active periods they carried out a number of routine chores connected with the maintenance of the laboratory. They were fed a diet of known composition which was adequate in protein, calories and vitamins.

The general plan of the experiment included a period of physical conditioning, 3 weeks of bed rest and 6 weeks of reconditioning. In the bed rest period the men were under constant supervision and bedfast nursing care. They were allowed up 10 minutes a day for bowel movements. Complete inactivity was enforced for an hour in the morning, two hours in the afternoon and for one hour after supper. Lights were turned out at 10 P.M. The subjects were encouraged to read, but a limit was put on letter writing; visitors were restricted to an hour a day and no 'occupational therapy' was allowed. The men underwent bed rest in pairs, starting in early March and ending in June. Two men (*D. M.* and *R. M.*) were in bed for 4 weeks.

A conditioning program lasting approximately 6 weeks was carried out before each period of bed rest. The men walked on a motor driven treadmill at 3.5 miles per hour and a 10 per cent grade 6 days a week. This rate of work demands an oxygen consumption of roughly eight times the basal metabolic rate. In addition, the men ran for 3 minutes at 7 miles per hour and 10 per cent grade. The conditioning program consisted of increasing the daily walks and runs according to the schedule presented in table 1.

Conditioning (training) in the psychomotor area was also included in the program. In a preliminary session the principles of psychomotor testing were explained, the importance of standardization of work methods was discussed and the subjects tried out the tests. Each subject received systematic practice in the course of 8 subsequent sessions, separated by one to two days. In each session all tests were performed twice, except for the strength measurements which were made in triplicate. This amount of practice allowed the subjects to

reach or closely approach a practice plateau. In the succeeding weeks the men continued to practice the tests at less regular intervals. Because the experiments could be performed with only 2 subjects at a time, the total number of practice sessions was not identical for all 3 pairs of subjects. However, in all cases a relatively stable performance level was secured before the beginning of the bed rest regimen.

Psychomotor functions differ in the degree of improvement with practice. The more the skill factor is involved, the greater the potential improvement. This is documented by figure 1 indicating a large amount of improvement in measurements involving fine coordination and lack of substantial improvement in functions of simple speed and of strength. In order to express the increments in comparable units, the standard error of measurement is used in figure 1.[2]

TABLE 1. ACTIVITY SCHEDULE OF SUBJECTS BEFORE AND AFTER BED REST

		WEEKS					
		1	2	3	4	5	6
Pre-bed rest	Hours of walk/day	1	2	2	3	3	4
	3 min. runs/wk.	2	2	2	4	5	4
Post-bed rest	Hours of walk/day	1	1½	2½	3	3	3
	3 min. runs/wk.				3	3	3
	2 min. runs/wk.			2			
	1½ min. runs/wk.	5	4	2			

Week no. 6 gives activity of men just before bed rest and week no. 1 presents activity during the 1st week after getting out of bed. Walking was done at 3 5 miles/hr. and 10% grade. Runs were carried out at 7 miles/hr. and a 10% grade.

The diet was adjusted to maintain caloric balance as estimated from body weight. This turned out to be 3400 to 3600 calories a day during the period in which the men walked one hour a day on the treadmill. As the conditioning program proceeded the caloric intake was increased until a level of 4400 calories a day was reached. In the same way, the diet during the reconditioning period was increased from 2300 to 2600 calories a day during bed rest to an intake of 4000 calories a day.

Standard clothing was worn for all tests and all cardiovascular measurements were carried out in air-conditioned rooms maintained at 78° F. and 50 per cent relative humidity. A test sequence was set up and adhered to throughout the entire series. The men arose without breakfast and the tests were carried out in the following order: Postural adjustment, roentgenkymogram of the heart, basal metabolism, the aerobic work test, 10-minute rest and the

[2] The value is obtained as the square-root of the 'random variance.' For derivation and computational formulae see reference 22.

anaerobic work test. The psychomotor battery was performed in the afternoon at a constant time after lunch in the sequence: Pattern tracing (coordination), ball pipe (speed of medium movements), tapping (speed of small hand movements), reaction time (speed of gross body movements), hand grip, back lift and ataxiameter. Blood volume (15) and cardiac output estimations were done on separate days.

METHODS

The size of the heart was estimated from roentgenkymograms by the method of Keys *et al.* (16). Total projection area and transverse diameter were measured in systole

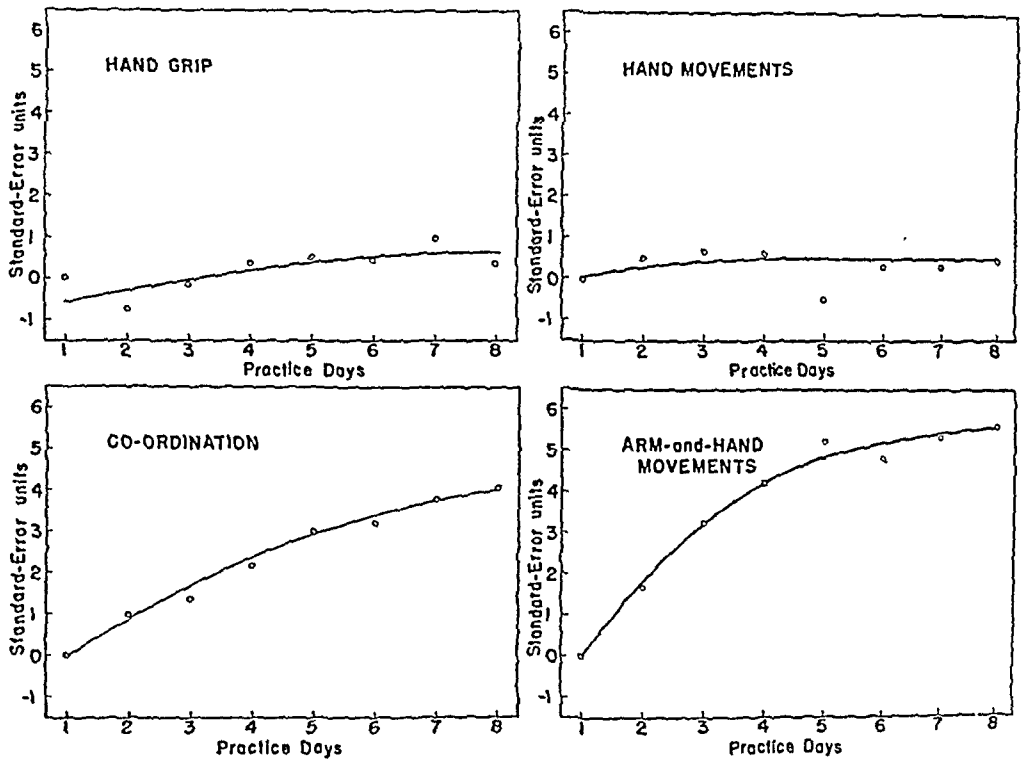

Fig. 1. EFFECT OF PRACTICE on 4 psychomotor tests. Hand grip was measured by the hand dynamometer; speed of hand movements, by a two-plate tapping test; coordination, by the errors in a pattern tracing test; and speed of arm and hand movements, by the ball pipe test. Standard error units are explained in the text.

All measurements were corrected for triangular distortion. Cardiac output was estimated by the acetylene rebreathing method of Grollman (17). The subjects were carefully practiced in the technique some days before the actual measurement. Gas samples were taken between 10 and 12 seconds and 20 and 22 seconds of rebreathing. The gas was analyzed in a Haldane gas analysis apparatus adapted to the determination of acetylene.

The cardiovascular response to posture was determined on a tilt table equipped with a footboard. Pulse rates and blood pressures were taken at one-minute intervals with the subject supine on the tilt table until both pulse and blood pressure reached a plateau. The subject was then tilted to 68° and pulse rates and blood pressures were taken every minute for 15 minutes. Supine and tilted pulse and blood pressure readings were averaged separately for presentation. Scores were calculated from the data by the method of Crampton (18).

Walking pulse rates were obtained near the end of a 30-minute walk on the motor driven treadmill at 3.5 miles per hour and 10 per cent grade. Pulse rates were counted with a stethescope placed at the apex of the heart for 15-second periods at 25, 28 and 30 minutes. The three values were averaged to give the work pulse rate. Expired air was collected in a balanced gasometer from 20 to 25 minutes of the walk. A sample was analyzed for oxygen and carbon dioxide in the Haldane apparatus.

Exhausting physical work consisted of running at 7 miles per hour for 90 seconds on a 15 per cent grade. Expired air was collected continuously during the run and for 90 minutes of recovery. The recovery collections were divided into three parts from zero to 10, from 11 to 24, and from 25 to 90 minutes after the end of the run. Blood for lactate determinations was taken at 12, 15 and 25 minutes of supine recovery; the lactate concentration was determined by the method of Edwards (19).

The psychomotor battery has been described in detail elsewhere (20). Strength was determined by the back lift and hand grip dynamometers. Coordination was measured by a pattern tracing test in which the speed of tracing was kept constant. The scores consisted of the number of contacts (errors) between the stylus and the side of the pattern and the total duration of these contacts. Speed of gross body movements (bending and reaching) was included in the choice reaction-time test. The values reported here are the averages of 50 reactions. Speed of medium movements involving the arm and hand was measured by the ball and pipe test (21) and speed of small hand movements by a 2-plate tapping test.

TABLE 2. EFFECT OF BED REST ON BASAL METABOLISM, CARDIAC OUTPUT AND HEART SIZE

FUNCTION	BEFORE	AFTER	Δ	PER CENT
B M.R., cc. O_2/min...	228	208	−20	−8.8
Stroke volume, cc.	82	80	−2	
Cardiac output, l/min.	4.62	4.71	+0.09	
Transverse diameter of heart, cm.	11.86	10.87	0.99	−8.3
Systolic heart volume, cc.	565	469	−96	−16.9

The amount of body sway during 2 minutes, with the eyes closed, was determined by an ataxiameter.

RESULTS

Circulation at Rest. The effects of bed rest on the basal metabolism, cardiac output and heart size are presented in table 2. It will be noted that there was a small decrease in the B.M.R., no change in the cardiac output and a definite decrease in both the transverse diameter and the heart volume. The change in the heart size must be regarded as highly significant since it decreased in every case.

The basal pulse rate, counted before breakfast and after the two-hour quiet period in the afternoon, showed a significant progressive increase which averaged roughly one-half beat per day of bed rest (table 3). The change tended to be larger in the afternoon counts than in the morning. The pulse rates counted in conjunction with the cardiac output estimates showed a much smaller change (mean = +2.7 beats); apparently the manipulations of the re-breathing procedure abolished much of the bed rest effect.

TABLE 3. PULSE RATE IN BED BY AVERAGES OF SUCCESSIVE TWO-DAY PERIODS FOR 6 NORMAL YOUNG MEN

DAYS	TIME	G. W.	L. B.	D. M.	R. M.	E. S.	A. W.	ALL
1–2	A.M.			51.0	48.0	44.0	45.0	47.0
	P.M.	62.0	53.5	56.0	53.0	45.0	55.0	54.1
3–4	A.M.	51.5	47.5	48.5	45.0	43.0	47.5	47.2
	P.M.	66.5	58.0	55.0	55.5	43.0	48.0	54.3
5–6	A.M.	50.0	44.0	50.0	52.0	42.5	44.5	47.2
	P.M.	67.0	50.5	56.0	58.0	46.0	57.5	55.0
7–8	A.M.	56.5	47.5	53.5	53.5	46.0	47.5	50.8
	P.M.	74.0	54.0	58.0	63.5	50.0	54.0	58.9
9–10	A.M.	56.5	50.5	53.0	52.0	46.0	49.0	51.2
	P.M.	63.0	57.0	55.5	64.0	50.5	53.5	57.3
11–12	A.M.	60.5	51.5	59.5	54.5	47.0	46.5	53.3
	P.M.	65.0	59.5	55.0	59.0	53.0	51.5	57.2
13–14	A.M.	54.0	51.0	57.5	45.5	47.0	47.0	50.3
	P.M.	69.0	57.5	63.5	65.5	52.5	57.0	60.8
15–16	A.M.	58.0	48.0	58.5	49.0	44.5	50.5	51.4
	P.M.	80.5	61.5	67.0	62.5	50.5	59.0	63.7
17–18	A.M.	57.5	58.0	61.0	57.0	46.0	43.0	53.8
	P.M.	77.5	61.0	70.5	66.0	50.5	57.0	63.8
19–20	A.M.	54.5	53.5	57.0	59.5	43.5	49.0	52.8
	P.M.	77.0	61.0	69.5	75.0	52.0	55.5	65.0
21	A.M.	62.0	54.0	62.0	62.0	50.0	53.0	57.2
	P.M.	81.0	70.0	69.0	70.0			72.5
Mean Δ/day	A.M.	+0.35	+0.55	+0.65	+0.53	+0.17	+0.23	+0.41
	P.M.	+0.88	+0.57	+0.89	+0.88	+0.46	+0.32	+0.67
F Value	A.M.	5.19[1]	15.39[2]	22.19[2]	6.31[1]	2.63	4.01	9.29[1]
	P.M.	6.66[2]	11.83[2]	28.36[2]	27.81[2]	18.00[2]	5.13[1]	17.97[2]

Pulse rates were counted at 8:30 A.M. under basal conditions and at 3:30 P.M. after 2 hours of supervised bed flat rest. These are the 'A.M.' and 'P.M.' values. The line marked mean Δ/day presents the average pulse rate increase per day of bed rest. The F value is the result of the F test used to determine the significance of the ratio of the variation attributable to linear regression to the variation attributable to deviations from regression.

[1] Significance at the 5% level. [2] Significance at the 1% level.

TABLE 4. EFFECT OF BED REST ON RESPIRATORY EFFICIENCY, OXYGEN CONSUMPTION, RESPIRATORY QUOTIENT AND MECHANICAL EFFICIENCY BEFORE AND AFTER BED REST

	BEFORE	AFTER	Δ	PER CENT Δ
Respiratory efficiency	55.3	46.1	−9.2	16.6
O_2 intake, l/min	2.003	1.913	−0.090	4.5
Respiratory quotient	0.82	0.93	+0.11	
Mechanical efficiency, %	16.20	16.29	+0.09	0.05

Work Performance. The efficiency of grade walking on the motor driven treadmill was not influenced by 3 weeks of bed rest. The mechanical efficiency,

together with the respiratory quotient (R.Q.) and oxygen intake per minute, is presented in table 4. The rise in the R.Q. after bed rest is in accord with the accepted principle that as physical work becomes more strenuous the R.Q. in work increases. Subjectively, the men found the half-hour walk more difficult after their period of bed rest. The calculated mechanical efficiency was low because the external work done was calculated as the amount of vertical lift in grade walking and no account was taken of the cost of horizontal travel. Table 4 also includes data on the respiratory efficiency, i.e. the oxygen removed

TABLE 5. PULSE RATES IN AEROBIC WORK BEFORE AND AFTER 3 WEEKS OF BED REST

SUBJECT	PRE-BED REST		DAYS OF RECOVERY									FINAL
			1	2	3	4	5	8	9	15	16	
D. M.	135	139	174	167	160	154	139	151	141	153	143	134 (49)
R. M.	127	126	171	156	145	149	145	149	150	152	140	118 (49)
E. S.	121	121	162	162	153	145	141	145	141	140	138	122 (72)
A. W.	139	129	167	174	163	150	142	157	152	155	155	120 (72)
L. B.	117	120	163	152	147	143	139	151	145	147	137	118 (36)
G. W.	121	125	167	161	156	147	144	151	147	146	139	128 (36)
Av.	127	127	167	162	154	148	142	151	146	148	142	

Rates are the averages for the last 5 minutes of a 30-minute period of walking at 3.5 miles/hr. on a 10% grade. The number of days of 'recovery' after which the 'final' values were obtained is indicated in parentheses.

TABLE 6. OXYGEN COST OF RUNNING ON A 15 PER CENT GRADE AT 7 MILES PER HOUR FOR 90 SECONDS BEFORE BED REST AND DURING RECOVERY FROM BED REST

	BEFORE	AFTER	1 WEEK	2 WEEKS
Work oxygen	3.712	3.318	3.300	3.460
Recovery oxygen	9.860	10.810	10.410	10.132
Total oxygen	13.573	14.126	13.712	13.592

Data are based on 4 men. All values are in liters of oxygen consumption less basal oxygen intake for designated period.

from each liter of inspired air. A definite inefficiency in the removal of oxygen from inspired air during work is produced by bed rest.

The effect of bed rest on the pulse rate during grade walking is presented in table 5. The dramatic rise in work pulse rate is one of the largest increases caused by stress which has come to our attention. It will be noted that the increase due to bed rest had been reduced by only 50 per cent at the end of 16 days of recovery. Examination of the final values indicates that this function had returned to normal some time before 36 days.

The oxygen cost of running up a 15 per cent grade at 7 miles per hour for the 4 men on whom satisfactory measurements of oxygen debt were obtained

is presented in table 6. If an overall R.Q. of 1.0 is assumed for this rate of work, the cost of the anaerobic work was increased by 556 cc. of oxygen or 4 per cent. At the end of 2 weeks of recovery, the men were able to perform the task with the same mechanical efficiency as before bed rest.

The capacity of the cardiovascular respiratory system to deliver oxygen to the muscles under stress was measured by the oxygen intake during the 90 seconds of running. Detailed data are presented in table 7. The average oxygen intake during the actual run was reduced by 730 cc. or 16 per cent. Recovery

TABLE 7. OXYGEN INTAKE IN LITERS DURING RUN ON 15 PER CENT GRADE AT 7 MILES PER HOUR BEFORE AND DURING RECOVERY FROM BED REST

SUBJECT	DAYS AFTER BED REST				
	Before	2	9	16	Final
R. M.	4.61	3.50	3.75	3.87	
D. M.	3.93	3.63	3.78	4.00	
A. W.	7.41	5.75	6.75	6.82	7.36 (72)
E. S.	4.47	4.04	4.13	4.14	4.38 (72)
L. B.	3.19	3.35	2.81	3.11	3.39 (36)
G. W.	3.55	2.56	2.68	2.83	3.76 (36)
Mean	4.53	3.80	3.98	4.13	

All men ran 90 seconds except *A. W.* who ran 2 minutes. Time, in days, of the final observation is given in parentheses.

TABLE 8. MAXIMAL OXYGEN INTAKE IN TWO MEN BEFORE AND AFTER BED REST

SUBJECT	BEFORE BED REST		AFTER	Δ	PER CENT
	10%	12.5%	10%		
R. M.	4.15	4.02	3.25	−0.90	21.7
D. M.	3.54	3.50	3.07	−0.47	13.3
Average	3.85	3.76	3.18	−0.67	17.4

Expired air was collected between 1′45″ and 2′45″ of a 3-minute run at 7 miles/hr. and at the grade indicated in the table.

was not complete after 16 days of post bed rest activity but appeared to be normal at 36 days.

True maximal oxygen intakes under standard conditions were determined on 2 subjects before and after bed rest. In this test the expired air is collected after the oxygen intake has reached a plateau, i.e. between 1′45″ and 2′45″ of a run at 7 miles per hour. The grade selected gave 'maximal' oxygen intakes since a further increase in grade did not produce any increase in oxygen intake. The data presented in table 8 show that the maximal oxygen intake was reduced by 17 per cent in these two men. It is clear that the cardiovascular-respiratory system was impaired by bed rest both in its ability to accelerate

the delivery of oxygen to the tissues and in the maximal amount that it could provide under standard conditions after the acceleration phase was completed. The effect of bed rest on the lactate concentration in the blood after running at 7 miles per hour up a 15 per cent grade for 90 seconds is presented in figure 2. Part of the change after bed rest must be attributed to the small increase

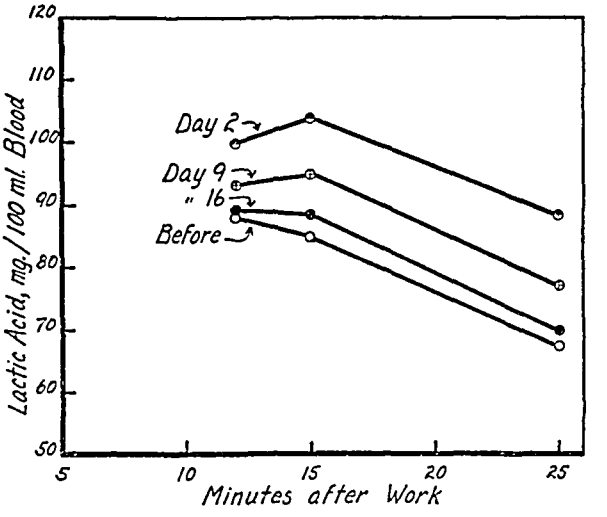

Fig. 2. Effect of bed rest on the lactic acid concentration in the blood after running for 90 seconds on the treadmill at 7 miles per hour and 15% grade.

Table 9. Average pulse rate and systolic blood pressure responses to tilting to 68° on tilt table (including the Crampton postural adjustment 'score') of six men before and during recovery from bed rest

Condition	Measurement	Control		Days of recovery from bed rest						Final[1]
				1	2	8	9	15	16	
Supine	Pulse rate, beats/min.	50	51	65	62	58	57	61	60	52
Tilted		63	64	102	89	90	86	84	81	71
Difference		13	13	37	27	32	29	23	21	19
Supine	Systolic B.P., mm. Hg	113	113	120	113	115	110	114	110	112
Tilted		111	113	106	109	109	109	107	108	109
Difference		2	0	14	4	6	1	7	2	3
Crampton score		56	63	−2	33	21	39	23	44	46

[1] See table 10 for time interval.

in the cost of the work. The blood lactate following exhausting work had returned to normal two weeks after resuming activity.

Response to Posture. The cardiovascular response to posture was poor after bed rest. The tilted pulse increased 38 beats per minute and the tilted systolic blood pressure decreased 6 mm. Hg. The postural adjustment score decreased dramatically. The results are presented in table 9. In spite of the

fact that the men were tilted for 15 minutes none of them fainted either before or after bed rest. However, after bed rest all men showed such signs of increased autonomic nervous system activity as increased palmar sweating, pallor and restlessness. The individual values of the postural adjustment scores are presented in table 10. It is apparent that recovery of the original response to posture after bed rest was slow and probably took place between 49 and 72 days after getting out of bed.

The effect of bed rest on the maintenance of a steady vertical posture was studied by means of the ataxiameter. Since the test was carried out with the

TABLE 10. POSTURAL ADJUSTMENT SCORES (CRAMPTON) BEFORE AND DURING RECOVERY FROM BED REST[1]

SUBJECTS	CONTROL	DAYS OF RECOVERY FROM BED REST					FINAL
		1	8	9	15	16	
R. M.	70	5	20	25	35	40	48 (49)
D. M.	60	15	25	30	40	45	52 (49)
A. W.	65	−35	15	55	10	35	60 (72)
E. S.	55	5	20	45	35	40	70 (72)
L. B.	70	−15	0	30	−10	45	20 (36)
G. W.	55	15	45	50	30	60	30 (36)
Mean	62.5	−1.7	20.8	39.2	23.3	44.2	46.7

[1] Time in days of the final observation is given in the parentheses.

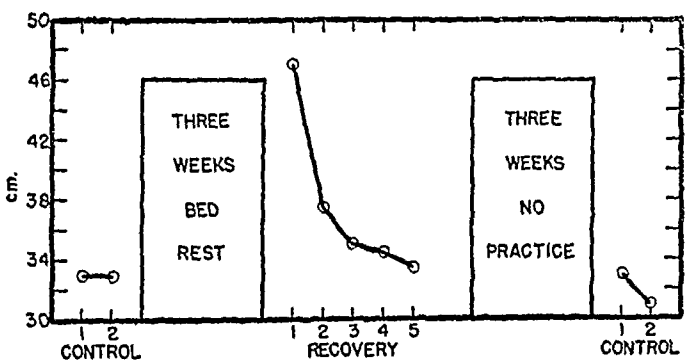

Fig. 3. EFFECT OF BED REST on total sway in centimeters as measured by the ataxiameter during a 2-minute period of standing with the eyes closed. The observation 5 days after arising from bed was followed by 3 weeks of no practice to demonstrate that lack of practice for this time period had no influence on the observations immediately following bed rest.

eyes closed the influence of the visual cues, which are important in the maintenance of the upright posture, are not measured by the procedure. The results are presented in figure 3. Bed rest produced a marked increase in the total sway of the individual during the 2 minutes of quiet standing but the pre-bed rest condition was attained at the end of 5 days of recovery. Since the score attained on the ataxiameter is susceptible to practice an objection could be raised that the observed change might have been related to the fact that no tests were made during the 3-week period of bed rest. To test this possibility a period of 3 weeks of no practice was inserted in the schedule after the men

had reached their control value. The test was then repeated and it will be noted in figure 3 that the period of no practice had no effect on the score.

Psychomotor Tests. The results of psychomotor tests are presented in table 11. The only items in this group that changed during bed rest were strength as measured by the back lift and coordination as measured by the number of errors in the pattern tracing test. Both items had essentially returned to normal by the end of the 1st four days of post bed rest activity. That lack of practice per se during bed rest was not the cause of the deterioration of these functions is evident from the failure of a 3-week no-practice period to produce any change (table 11).

TABLE 11. RESULTS OF PSYCHOMOTOR TESTS

	DAYS	STRENGTH			SPEED OF MOVEMENT		
		Hand grip	Back lift	Coordination	Gross arms and body	Medium arms and hand	Small hand
Pre-bed rest	1	61	180	64	45	65	62
	2	60	183	64	45	65	61
Post-bed rest	1	59	168	76	48	63	60
	2	59	167	75	47	63	62
	3	61	172	68	46	64	63
	4	62	175	64	46	65	64
Control period	26	62	184	56		64	62
	27	63	186	56		66	62

Strength was measured with standard dynamometers and expressed in kilograms. Coordination, as measured by the pattern tracing test, is expressed as the number of contacts between the stylus and sides of the path in one tracing of the pattern. Speed of gross (arm and body) movements is expressed as the average time, in 1/120 sec. of 50 reactions. Speed of medium (arm and hand) movements as measured by the ball-pipe test is expressed as the number of times a steel ball was passed through a one-foot pipe in one minute. The speed of small (hand) movements as measured by the 2 plate tapping test is expressed as the number of taps in 10 seconds. Good performance is indicated by larger values in hand grip, back lift and the tests of speed of medium and small movements.

Herniorrhaphy. When *subject E. S.* arrived at the Laboratory he had a hernia which was in need of repair. It was decided to take advantage of this situation and to compare the effects of uncomplicated bed rest and that of bed rest plus surgery. Three months of reconditioning after the standard tour in bed rest were allowed to insure complete recovery from the deconditioning induced by bed rest alone. The standard pre-bed rest tests were carried out with the exception of the back lift and the anaerobic work. After the herniorrhaphy the subject followed the same routine as he had in bed rest, ate the same food, and began active convalescence exactly 3 weeks after the operation. Performance tests were carried out for 15 days after arising from bed.

TABLE 12. COMPARISON OF EFFECTS OF BED REST AND HERNIORRHAPHY ('OPERATION') PLUS BED REST ON BODY WEIGHT, PULSE, OXYGEN CONSUMPTION, AND RESPIRATORY EFFICIENCY AT END OF HALF-HOUR WALK AT 3.5 MILES PER HOUR AND 10 PER CENT GRADE

FUNCTION	CONDITIONS	BEFORE BED REST (DAYS)	RECOVERY (DAYS)		
		1	1	9	15
Weight, kg.	Bed rest	175.0	173.0	175.5	175.0
	Operation	175.0	168.0	174.0	176.0
Walking pulse, beats/min.	Bed rest	121	162	141	140
	Operation	118	168	136	140
Walking O_2 intake, l/min.	Bed rest	2.07	1.97	2.00	2.01
	Operation	1.90	1.82	1.94	1.91
Respiratory efficiency	Bed rest	53.6	44.2	49.7	51.7
	Operation	50.2	41.6	47.6	52.1

TABLE 13. COMPARISON OF CARDIOVASCULAR RESPONSE TO POSTURE BEFORE AND AFTER BED REST AND HERNIORRHAPHY IN SUBJECT E. S.

FUNCTION	CONDITIONS	BEFORE BED REST (DAYS)	RECOVERY (DAYS)		
		1	1	9	15
Resting pulse, beats/min.	Bed rest	48	58	48	42
	Operation	42	48	42	44
Resting systolic B.P., mm. Hg	Bed rest	120	120	120	120
	Operation	122	122	116	126
Resting diastolic B.P., mm. Hg	Bed rest	84	82	70	68
	Operation	82	86	88	78
Tilted pulse, beats/min.	Bed rest	60	97	76	70
	Operation	54	102	60	58
Tilted systolic B.P., mm. Hg	Bed rest	117	111	118	117
	Operation	117	107	113	121
Tilted diastolic B.P., mm. Hg	Bed rest	94	89	87	85
	Operation	89	94	91	91

TABLE 14. COMPARISON OF EFFECTS OF BED REST AND HERNIORRHAPHY IN SUBJECT E. S. ON PSYCHOMOTOR TESTS

FUNCTION	CONDITIONS	PRE BED REST (DAYS)		POST BED REST (DAYS)						
		1	2	1	2	3	4	5	16	27
Hand grip	Bed rest	66	62	62	62	62	62	62	62	64
	Operation	60	60			54.8	58.5	57.5	58.5	57
Coordination	Bed rest	89	86	102	106	100	90	80	75	78
	Operation	70.5	65.0			90.5	75.7	82.5	74	85.5
Gross speed	Bed rest	52	54	56	52	53	53	51		
	Operation	61	62			65.3	64.6	63.7	58.7	59.6
Medium speed	Bed rest	61	62	63	64	64	64	64	64	64
	Operation	65.5	66.5			65.5	66.5	64.8	66.3	66.3
Small speed	Bed rest	60	60	60	60	62	64	64	64	66
	Operation	63	61				65.2	61.8	58.5	71.3
Body sway	Bed rest	36.0	39.5	54.5	49.0	47.5	41.5	41.5	42.5	36.5
	Operation	38.0	36.5	51.5	44.0	39.5	38.0	43.0	42.5	

Line headings and units are explained in title of table 11.

The results are presented in tables 12, 13 and 14. The increased stress of bed rest plus herniorrhaphy over that of bed rest alone was reflected in small increases in the work pulse and the tilted pulse, in small decreases in the grip strength and in a deterioration of performance in the coordination test. However, the deconditioning produced by bed rest plus herniorrhaphy was of the same order of magnitude as that produced by bed rest alone and the rate of recovery after bed rest plus herniorrhaphy did not differ materially from that after bed rest alone.

DISCUSSION

The New York Experiment. An important study on experimental bed rest was reported recently by Deitrick, Whedon and Shorr (10). In comparing the present results with those of the New York group, several differences in the experimental conditions must be noted. The 4 young men studied in New York were immobilized in bivalve casts extending from the umbilicus to the toes. Except for some 30 to 40 minutes daily, the casts were in place for 6 to 7 weeks. There was also a major difference in the dietary plan. With the Minneapolis subjects, the caloric level of the diet was adjusted to the activity level with the result that the body weight was maintained constant in the control period on an intake which varied from 3400 to 4400 calories a day and in the bed rest period on an intake of 2300 to 2400 calories daily. The New York subjects, however, received the same diet at all times, this being set at the balance level for the control period before bed rest; this provided 2500 calories daily for one man and 2800 calories for each of the other three subjects. During the control period the New York subjects were not only up and about; they took one-hour walks three to four times a week and had a daily schedule of 30 minutes of calisthenics and 30 minutes of swimming. However no estimate of the energy expended in these activities was provided. It would be expected that the difference in overall energy expenditure between immobilization and the control period would be very substantial. However, the data presented by the New York group indicate that this difference was in fact very small. The subjects in the New York group did not gain weight during their 6-week period of immobilization. Deitrick *et al.* suggested that the weight constancy of their subjects was "probably the result of the simultaneous loss of muscle protoplasm and storage of fat or carbohydrate" (10). If we accept this hypothesis and the recorded food intakes of the New York subjects, we can calculate that the difference in total energy expenditure between the control period and immobilization must have been only of the order of 350 calories a day. This is a very slight reduction in energy expenditure but is not incompatible with a change in activity confined to a localized area of the body. There is no doubt that a significant degree of localized immobilization was obtained by the New York group. Their data give clear evidence that actual atrophy of the muscles in the lower extremities was achieved.

In spite of these differences, many of the results were closely similar in the two groups. There was a common loss of tolerance to exercise and vertical stance and essentially no change in grip strength. The New York subjects suffered a loss of strength in the leg muscles, notably the anterior tibial and the gastrocnemius-soleus group. These muscles were not studied at Minneapolis but our subjects showed some decline in back strength. Our subjects lost an average of 1.76 grams of nitrogen per day in bed rest (12) as compared to an average of 1.58 grams for the New York subjects in the first 3 weeks of immobilization.

The small activity-immobilization total energy expenditure difference may well account for the smaller basal pulse rate and blood volume (15) changes which were found in New York as compared to Minneapolis. The failure to find a change in the heart size in the New York subjects is not surprising because apparently no serious effort was made to obtain quantitative data.

General Comment. Coordination, speed, strength and endurance are the fundamental components of fitness. Since no single test samples the performance of all these functions, a battery of tests was used which covers the several components of fitness. The rationale for this approach has been discussed elsewhere (23). We wish to emphasize that a high degree of conditioning has been attained in each of the several tasks employed as test situations before the men entered upon bed rest.

The deterioration of cardiovascular function in our subjects may be somewhat larger than one would find in the completely sedentary individual who has spent an equal amount of time in bed. Our subjects experienced feelings of tiredness on getting out of bed. It is apparent that there is a minimum degree of cardiovascular fitness which is necessary to carry on even a sedentary occupation without fatigue. The evaluation of this degree of fitness must await further work.

One might inquire whether the negative nitrogen balance which was present during bed rest played an important rôle in the loss of fitness which these men suffered. It is obvious that if such a negative nitrogen balance were continued for an indefinite period a large loss of strength would result. However, it can be stated that a nitrogen loss per se of the order of magnitude sustained by our subjects (an average total of 37 grams of nitrogen, corresponding to about 1 kg. of muscle) does not necessarily play an important rôle in the loss of fitness. Studies on the effects of complete starvation and hard work showed that men who had lost 30 to 40 grams of nitrogen during a 5-day period of hard work without food recovered their fitness within 5 days (24).

Physical conditioning is always the result of activity, i.e. muscular exercise. The extent to which any of the principal components of fitness will improve during the conditioning process varies with the type of task which is employed to produce conditioning. In the present experiments a broad program

of conditioning was employed. Bed rest which implies nearly complete inactivity is in principle the converse of procedures which result in a high degree of fitness. Actually the deconditioning resulting from the bed rest was not a true reverse of the conditioning process since only one item, endurance (cardiovascular function), of the four components of fitness showed an important degree of deterioration.

The results reported here have a definite bearing on the intelligent planning of convalescent programs. In dealing with the deconditioned individual, the techniques and procedures used should be planned so that those systems which have undergone deterioration will be given the greatest activity (exercise) which is compatible with the patient's condition. It is obvious that many diseases present special problems in reconditioning but it is equally obvious that the common denominator in the deconditioning of most patients is bed rest. A reconditioning program for anyone who has undergone a prolonged rest in bed should employ methods which improve cardiovascular performance in work and the vertical posture. The success of the Army Air Forces reconditioning program (8, 25) is ample testimony that exercise within the capacity of the patient is the most efficient tool for the practical reconditioning of patients. This is in accord with our own results since even mild exercise places a greater stress on the circulation than on any other known factor. We insist that no conditioning will be achieved without placing some stress on the circulation. In this connection it may be mentioned that little is known of the effects of massage and heat in reconditioning the circulation.

The long persistence of poor cardiovascular adjustment to the upright posture after bed rest in spite of ample physical exercise indicates that the problem of posture should receive special attention. The successful use of the head-up bed in the treatment of postural hypotension (26) suggests that this procedure might be of use in a well planned convalescent program. Whedon, Deitrick and Shorr (27) have reported that the use of the Sanders' oscillating bed (28) during the period of immobilization reduced the loss of cardiovascular efficiency in the vertical stance and also favorably influenced some of the metabolic effects of bed rest such as the loss of nitrogen and calcium.

SUMMARY AND CONCLUSIONS

Six healthy young men whose ages were from 20 to 33 years were studied before, during and after a 3- to 4-week period of bed rest. Measurements were made under rigidly controlled conditions on the performance of the cardiovascular system (at rest, in the upright posture, and during work), and on speed, coordination and strength. A high degree of conditioning for the performance of all tests was achieved before the bed rest period.

Bed rest produced a 17 per cent decrease in heart volume and an 8 per cent decrease in the transverse diameter of the heart. There was a highly sig-

nificant increase in the resting pulse rate which average roughly 0.5 beats per minute for each day of bed rest. The pulse rate at the end of a half-hour walk at 3.5 miles per hour and 10 per cent grade increased by 40 beats per minute after bed rest. There was no change in the mechanical efficiency during this walk, as the result of bed rest.

The oxygen intake during a 90-second run at 7 miles per hour and 15 per cent grade was reduced by 730 cc. of oxygen or 16 per cent after 3 to 4 weeks of bed rest. This was accompanied by increases in oxygen debt and blood lactate after the run and a decrease in mechanical efficiency. The maximal oxygen intake was determined in 2 men who showed decreases of 13 and 22 per cent after bed rest.

Bed rest produced a marked deterioration in the cardiovascular response to posture as measured by pulse rate and blood pressure changes produced by tilting to 68° on a tilt table. Ataxiameter studies showed that a definite increase in sway resulted from bed rest. Coordination, as measured by pattern tracing, suffered a small loss as the result of bed rest while speed of small hand movements, of medium arm and hand movements and of gross body and arm movements showed no deterioration. Grip strength was not influenced by bed rest and back strength showed only a small deterioration.

After bed rest the rate of recovery of the various functions was roughly proportional to the extent of the deterioration in bed rest. Strength, coordination, and postural sway recovered early (4 days); blood lactate after exhausting work, and the oxygen cost of exhausting work recovered at an intermediate time (2 weeks); pulse rate during grade walking and O_2 intake during exhausting work recovered late (between 2 and 5 weeks), and the cardiovascular response to posture was very late in returning to normal (after 7 weeks). In one man the effect on the principal components of fitness of a herniorrhaphy with bed rest for 3 weeks was of the same order of magnitude as bed rest alone.

It is concluded that the deconditioning due to bed rest has special characteristics, with the major loss of performance occurring in the cardiovascular system.

We thank Dr. Clarence Dennis, Professor of Surgery, for performing the herniorrhaphy and providing conditions in the Hospital comparable to those in the Laboratory. It is a pleasure to acknowledge the conscientious cooperation of Donald Martinson, Ralph Michener, Adrian Wilson, Eugene Sunnen, Grant Washburn and Lynn Brown who served as subjects. Mr. Walter Carlson performed the gas analysis. Mrs. Angie Sturgeon Skinner, head technologist, Mrs. Nedra Foster, Dietitian, and Miss Francis Hannah, R.N., provided indispensable assistance.

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Effect of Submersion in Water on the Volume of Residual Air in Man[1]

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THE POSSIBILITY OF ESTIMATING the proportion of fat to other tissues in the body by measurement of the density of the body has been demonstrated (1). The principle of Archimedes is convenient for the measurement of density but in the case of intact man it is necessary to correct for the air in the lungs, even when the underwater weight is recorded at the end of maximal expiration. The most obvious source of error in the density measurement, and thereby in the indirect estimation of fat, is the uncertainty as to the volume of the residual air in the lungs at the time of weighing.

The data on residual air volume reported in the literature have been obtained under ordinary environmental conditions (in air). On theoretical grounds one might expect that with the subject completely immersed in water during the process of exhalation, the volume of residual air would be somewhat smaller than when determined in air. There is at least one indication that this may be the case (2). Hamilton and Mayo stated, incidental to another problem, that when a subject standing in water and forcing the air out of his lungs is allowed to sink and to complete the expiration at a depth of two to three feet, the pressure of the water against the thorax enables him to expel a volume of air larger than normal 'vital capacity.' The statement was not documented.

The present study was designed to provide quantitative information on the effects of submersion on the volume of residual air in man.

EQUIPMENT FOR WEIGHING SUBMERSED SUBJECTS

The scale assembly for weighing the subjects while submerged is illustrated in figure 1.[2] Suspended from the lower hook of the scales is a seat made from $\frac{1}{8}''$ stainless steel sheet hung from a frame of $\frac{1}{4}''$ stainless steel rods. The assembly is tared for weighing subjects submerged in water with the chair lowered so that the bottom of the hook that connects the frame to the scales just

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[2] Yale and Towne Co. 'Kron' no. 1850, 20 kg. x 20 gm.

touches the water level. The scale and seat assembly is raised and lowered by means of a 500-pound capacity electric hoist.

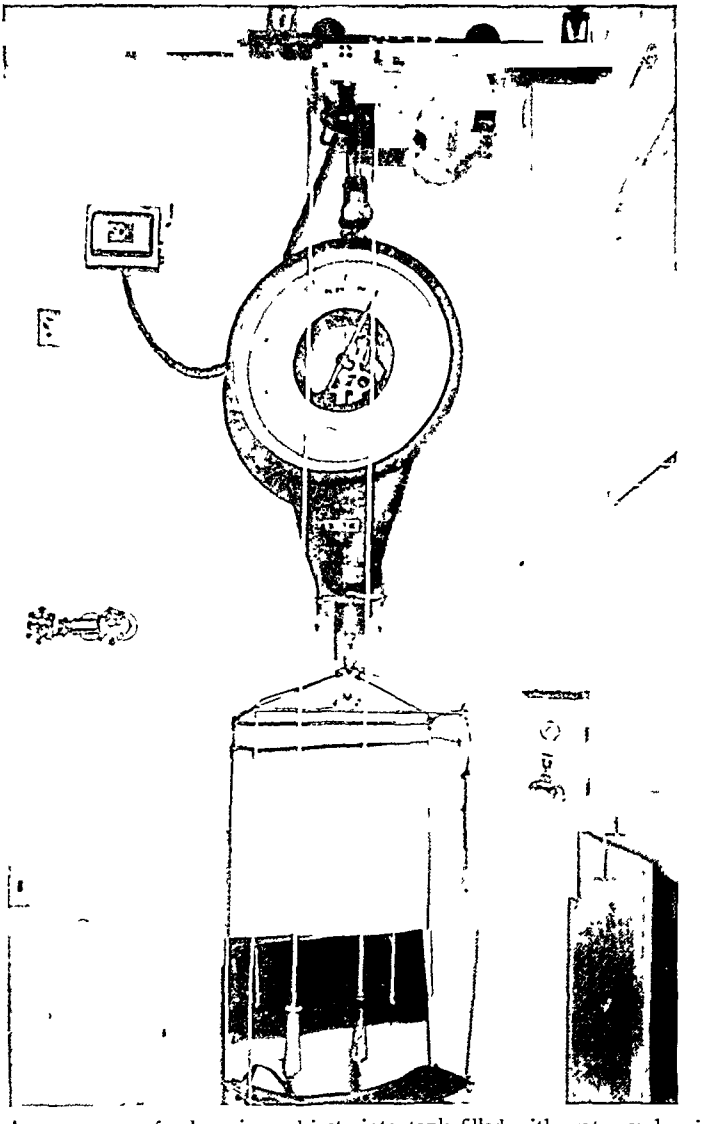

Fig. 1. ARRANGEMENT for lowering subjects into tank filled with water and weighing them submersed.

PROCEDURE

The volume of residual air was determined for subjects at complete expiration both while completely submerged in water and while seated in the room in which the under-water weighing was done. The open-circuit, nitrogen-

dilution method (3) was used with slight modifications necessitated by under-water determinations. The essential details of the equipment are illustrated in figure 2.

The Tissot gasometer is first thoroughly flushed with oxygen while the *valves A* and *D* are turned to allow the flow of the gas through the by-pass tube. After flushing they are turned to the position allowing the oxygen to reach *valve B*. The subject is seated in the weighing chair, with his nose clip adjusted to prevent breathing through the nose. A rubber mouthpiece, attached to the short pipe (between *valves B and C*), is inserted. The vital-

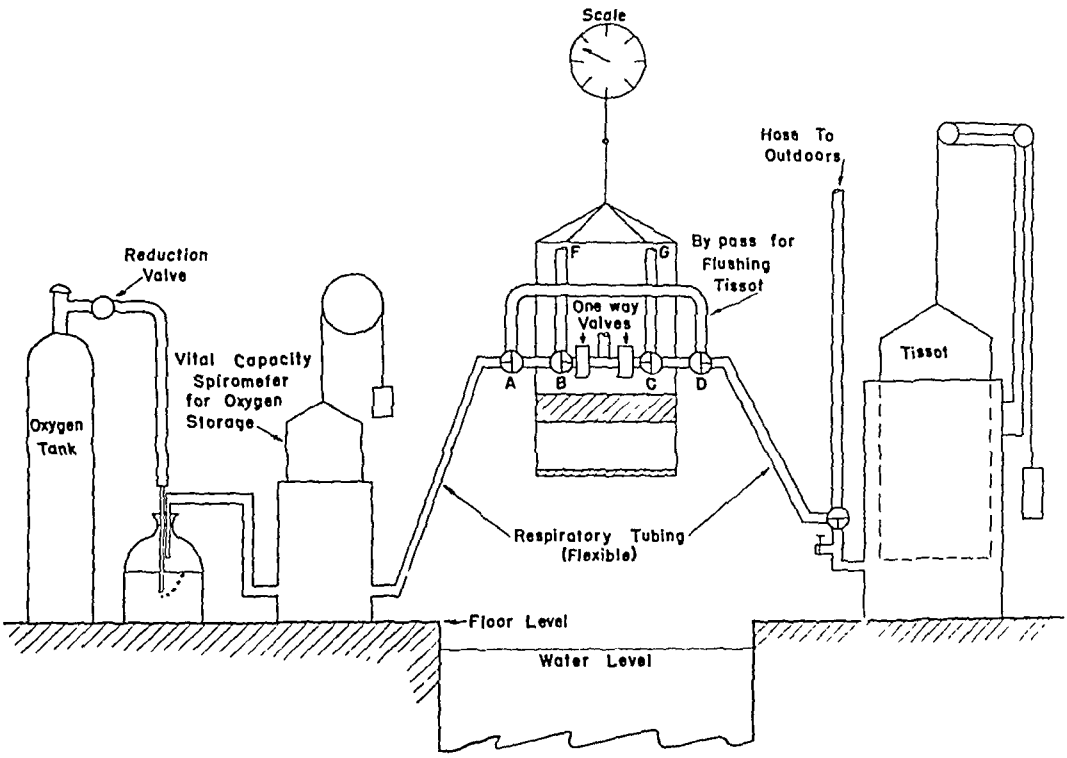

Fig. 2. DIAGRAM of equipment set up for determinations of residual air.

capacity spirometer is filled to allow for the first inhalation of O_2. The one-way *valves B* and *C* are turned to allow breathing of the room air.

Our customary procedure for density measurements was followed in connection with the determinations of under-water residual air. The subject is instructed to take in a moderate breath and then to exhale as he is lowered into the tank until the bottom of the hook on the weighing scale touches the water. The distance between the hook and seat of the chair is 96 cm. The temperature of water is kept at 36° ± 0.5°C. *Pipes F* and *G* extend above the water so that the subject does not exhale against pressure. Having completed the exhalation the breath is held for 3 to 5 seconds while the weight is read (to the nearest 100 gm.). Following this the subject is lifted above water and instructed to breath normally.

Three or more preliminary weighings are made to check the consistency of the under-water weight obtained after a forced, maximal expiration. If three preliminary weighings check within ± 100 grams it is concluded that the subject is 'trained' and may be relied upon to produce minimum values of the residual air volume in the actual determinations of the latter. On the fourth submersion, when the weight reaches the previously established level, *valves B* and *C* are turned, with the subject immersed and holding his breath, to allow inspiration of oxygen from the spirometer and expiration into the Tissot gasometer. After the valves have been adjusted, the subject is raised above water and allowed to breath oxygen for a period of 7 minutes. Oxygen which has been bubbled through water to assure saturation with water vapor is supplied to the spirometer at a rate required by the subject. After 7 minutes the volume of expired air in the Tissot gasometer is noted and samples for the analysis are drawn. After each determination the tubing and the gasometer are flushed six times with about 6 liters of oxygen. A hose connects the Tissot gasometer with the outdoors to prevent increasing the room air O_2 when flushing the tubing and the gasometer.

After the measurement has been completed the subject is allowed to dry himself and put on a bathrobe. He remains reasonably quiet for the next 30 minutes at which time the procedure is carried out, except that the subject is not immersed in water. The determinations were repeated about a week later.

The gas samples were analyzed in the Haldane apparatus using the nitrogen storage method (4) except that two pyrogallol chambers were used. One of them served to store 6 to 7 cc. of N_2 which was later brought into the sample when a sufficient amount of O_2 was absorbed. Duplicate analyses were made and the two values were averaged.

The residual air volume was calculated following Cournand *et al.* (3). The known dead space of the gasometer and the space between *valves B* and *C* were taken into account in the calculations. The amount of nitrogen excreted from the lungs during the period of breathing pure oxygen was estimated on the basis of data provided by Cournand, Yarmush and Riley (5).

Subjects. The 9 subjects were students with an age range from 18 to 28 years. All of them were in good physical health and of average body build; none was either grossly obese or emaciated.

RESULTS

The values obtained on two occasions for air volumes remaining in the lungs and the respiratory passages after a complete exhalation in air and under water are given in table 1. In 13 of 18 determinations the residual air volume was slightly smaller under water than in air.

For computational purposes the differences (d_1 and d_2) obtained for each individual ($N = 9$) on the two separate trials were combined. The last column

in table 1 represents these differences, d, defined for each individual as $d = (d_1 + d_2)/2$. The overall average difference, $\bar{d}$, was −129 cc. The results obtained in the two separate trials were fairly consistent within the individual subjects. This suggests that we are dealing with a real difference produced by submersion. However, the differences between individuals are relatively large. The F ratio, based on the 9 d values and equivalent to a t^2 for paired variates, is 4.96. For one and 8 degrees of freedom the F value is 3.46 at the 10 per cent level of significance and 5.32 at the 5 per cent level. The F value of 4.96 approaches but does not reach the 5 per cent level of statistical significance. Similar results were obtained when a more complex analysis of variance was applied. Consequently, one must suspend the judgment whether or not there is a difference between the two conditions under which the residual volume was

TABLE 1

SUBJECT	TRIAL 1			TRIAL 2			d
	A_1	W_1	d_1	A_2	W_2	d_2	
J.E.	1379	1436	+57	1448	1594	+106	+81.5
D.T.	1143	1119	−24	1026	1029	+3	−10.5
R.R.	1789	1375	−414	1786	1371	−415	−414.5
J.H.	1944	1847	−97	1916	1684	−232	−164.5
P.W.	1496	1566	+70	1472	1564	+92	+81.0
S.N.	2013	1725	−288	2067	1682	−385	−336.5
L.E.	1682	1479	−203	1607	1373	−234	−218.5
D.A.	1473	1365	−108	1531	1385	−146	−127.0
B.T.	1394	1337	−57	1199	1149	−50	−53.5
Mean	1590	1472	−118	1566	1426	−140	−129.0

Values, in cc., of the residual air volume determined above water (A) and during complete submersion (W); $d = \frac{d_1 + d_2}{2}$.

determined. Further work is necessary in order to uphold or disprove the hypothesis that residual volume decreases, on the average, in submersed subjects. On the basis of the available data it is not safe to generalize beyond the sample actually studied; the mean difference found here should be applied with caution to other groups.

The data in table 1 indicate that there are not only individual differences in the magnitude of the response to submersion but, in 2 subjects, the direction of the difference was reversed on both trials. Obviously, there is more than one factor determining the effect of submersion on residual air volume. The mechanical compression should help the subject to exhale more completely. On the other hand, the psychological effect of the submersion resulting, at least in some individuals, in a moderate degree of anxiety might inhibit the exhalation. We are unable to suggest any other important mechanisms and the

recorded differences must be considered as a resultant of the two factors. In subjects *J.E.* and *P.W.* (table 1) the psychological effect was predominant and produced a larger residual air volume under water.

The mean difference of 130 cc. between the residual volume obtained under the two conditions does not appear very large. What effect would it have on the specific gravity and the derived estimate of the percentage body fat had the 'air' rather than 'underwater' values been used? For our 9 subjects the average values of body weight in air = 78.006 kg., body weight in water = 3.800 kg., residual volume in air = 1.578 liters, residual volume in water = 1.449 liters. The average values of specific gravity are 1.074 and 1.072, respectively. According to the conversion tables worked out by Rathbun and Pace (6) these values of specific gravity correspond to 12.2 and 13.1 per cent of the body as fat.

Of interest is a slight drop in the average values obtained in the present series on the second trial under both conditions. The value for the residual volume determinations in air decreased from the first to the second trial by 24 cc., for the under-water determinations by 40 cc. This change may be regarded as a result of 'practice' in the procedure, resulting in a slightly more complete exhalation. These trial-to-trial changes were small and would not be considered statistically significant but they increase somewhat the apparent day-to-day variations in the residual air volume.

In the literature there is very limited information on the repeatability of the values obtained for residual air. Rahn, Fenn and Otis (7) reported an average intra-individual standard deviation of 84 cc. with a range from 57 to 101 cc. for 5 male subjects measured five times a week for 7 weeks. No comment was made as to the presence or absence of a practice trend. In our group the average intra-individual standard deviation of the values was 66 cc. for measurements done in air and 78 cc. for residual air volumes obtained on submersion.

SUMMARY

Determinations of the volume of residual air were made under ordinary conditions with the subjects exhaling in air, and during complete submersion. Nine normal young men served as subjects.

The average values, obtained in two sets of measurements made about a week apart indicated that the under-water values were smaller by 118 and 140 cc., respectively. There were large individual differences in the response to submersion and the overall average decrement of 129 cc. did not quite reach the 5 per cent level of statistical significance. Using the average values of residual volume determined in air rather than those obtained for submersed subjects would lower the estimated fat content of the body by less than one per cent.

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Quantitative Criteria of Oculomotor Performance and Fatigue[1]

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THE EYE MOVEMENTS, carried out under the control of two sets of six external eye muscles, are the resultant of a complex and coordinated neuromuscular activity (1–3). It may be expected that certain types of physiological stresses which result in neuromuscular deterioration will be reflected by this complex coordination mechanism with greater sensitivity than by the tests of simpler neuromuscular functions, such as grip strength or tapping. Analysis of photographic records of eye movements has been used intensively during the last 50 years as an objective approach to the study of ocular behavior, especially during reading (4, 5). In reading one is not aware of the rapid (saccadic) movements from fixation to fixation, the regressive movements, and the pauses between movements in which the perception of the printed material actually takes place. The 'involuntary' character of the eye movements in reading would seem to recommend the analysis of eye movements during reading for psychophysiological research. However, reading is a highly complex process, dependent on the nature of the text read and the individual's comprehension, and not suitable for several reasons, such as the difficulty of providing equivalent text samples, for studies in which a group of subjects is measured on several occasions.

The aim of the series of investigations reported in this paper was: *1*) to develop quantitative criteria for characterization of simple voluntary eye-movements; *2*) to obtain some indications of the magnitude of the day-to-day variation; *3*) to study changes resulting from continuing the eye movements at a rapid rate; and *4*) to determine the type and magnitude of changes present after hard visual work.

APPARATUS, PROCEDURE, SUBJECTS

The standard model of the ophthalmograph, manufactured by the American Optical Company (6, 7), was used for recording the eye movements. The instrument works on the principle of corneal reflection; the historical development of the technique was discussed by Carmichael and Dearborn (8). A narrow beam of light, coming into each eye from the outer side and from below

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the eye, is reflected from the corneal surface of the eyeball and, by means of an adjustable telescopic tube, is focussed on a 35 mm. film moving at a constant speed (one-half inch/sec.). During a lateral movement of the eyeballs the angle of the incident (and of the reflected) rays changes and the extent of the movement is registered on the film.

The head is held in place by an adjustable chin support and head clamps. During the 25-second periods used in the majority of our testing sessions little difficulty was encountered in having the subject maintain a steady position of the head. On the ledge, designed for holding a text sample in reading experiments, a white card was placed containing three targets: a cross in the lower part of the vertical midline, used at the start of the test for the measurement of the steadiness of the eyes during continued fixation, and two black dots, 3 mm. in diameter, with a white center, used as targets for successive eye movements. The distance between the two dots was 8.5 cm.; at a distance of 34 cm. from the midpoint between the eyes, this represents a visual angle of 14°16′. Because of the presence of slight differences in the apparent distance between the two target points on the film, the distance was recorded for each individual at the start of each session. The test performance consisted of a rapid succession of lateral movements of the eyes from one target to the other.

The subjects were 6 normal young men in good physical condition and with normal eyesight. At the end of each test the subject tested was identified by interrupting the beam of light for shorter or longer periods, thus marking the record with dots or dashes according to the code.

QUANTITATIVE CHARACTERISTICS OF EYE MOVEMENTS

An eye movement cycle consists of two parts: 1) the large and rapid (saccadic) movement of the eyes from one fixation point to the other and 2) the fixation of the target. It is known (9) that distinct perception does not take place during the saccadic movement; it is possible only when the optical image of the target remains stationary upon the retina. Actually, the eye rarely remains absolutely motionless during fixation; frequently small movements are present, which may be as a rule interpreted as adjustment movements having as their purpose a sharp focussing of the target point. The two basic characteristics of eye movements are duration and extent. A schematic analysis of an eye-movement cycle is presented in figure 1.

The total duration (τ) of an eye movement cycle consists of two components: the time of the movement phase ($\mu = \overline{BE'}$) and of the fixation phase ($\varphi = \overline{E'F'}$), expressed in 1/100 seconds. The extent of the saccadic movement is indicated by $m = \overline{EE'}$. This distance is to be compared to $d = \overline{RL}$, the true distance between the right and left target, determined during prolonged, sharp fixations of one and the other target point, R and L. The discrepancy between d and m, without reference to its direction, provides a measure of the precision

of a saccadic movement. In arriving at the score for an individual, the discrepancies obtained for single movements are averaged. Using the average value of m, the difference ($\bar{m} - d$) referred to as a relative (directional) deviation from target distance indicates the average amount of overshooting or undershooting of the targets.

The extent (range) of movement during 'fixation' ($f = \overline{FE''}$) may serve as a criterion of the precision and steadiness of fixation. As a rule, the corrective movements take place in one direction, as indicated in the figure. In some subjects, jerky movements may be observed. In all cases, the total range (distance between the limits of lateral movements during fixation) is taken as the score. The ratio of the average movement distance ($\bar{m}$), or its angular equiva-

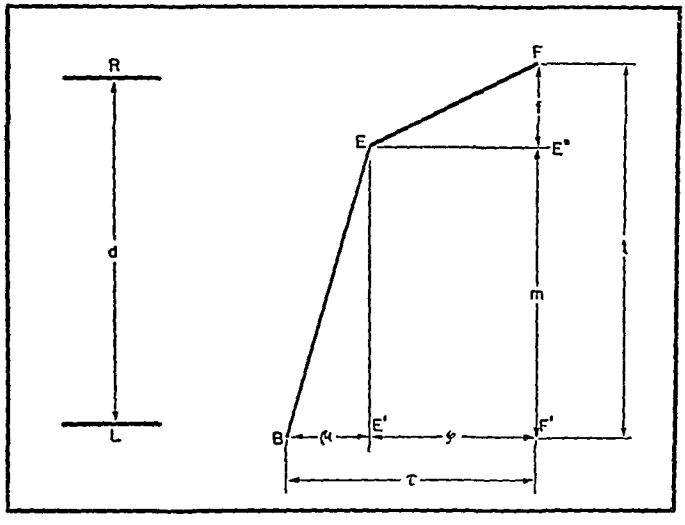

Fig. 1. Analysis of an eye movement cycle in reference to its temporal and spatial characteristics. For explanation see text.

lent, to the average time of the saccadic movement (μ) represents the velocity of the saccadic eye movements.

ANALYSIS OF THE EYE-MOVEMENT RECORDS

In analyzing the eye-movement records the film was projected on a 20 by 20 in. screen, calibrated in tenths of an inch; the enlargement factor was chosen so that the distance the film traversed within one second was made equal to 10 inches on the screen. Consequently, $\frac{1}{10}$ inch on the screen corresponded to $\frac{1}{100}$ second. This arrangement makes it possible to measure the time parameters of the eye movements with considerable precision. The spatial characteristics were measured in inches on the same scale and converted into angular values on the basis of the fact that 8.5 cm. distance between the targets

on the card, corresponding to a visual angle of 14°16′, was represented by 59.44 units on the screen. Consequently, one unit ($\frac{1}{10}$ inch) on the screen represents an angle of 14.4 minutes. This is only an approximative value as the beam of light reflected from the cornea is not displaced by a constant amount throughout the sweep of the eye.

For purposes of measurement of the repetitive movements, 6-second samples were generally used, except in subjects whose eye movements were very slow. In this case the length of the film measured was enlarged so as to include about 20 eye-movement cycles. The following procedure was followed in measuring the records. First, the total number of gross movements (movement-fixation cycles) within the given time interval was established. The movement distance (m), the duration of each fixation (φ) and the extent of corrective movements (f) during fixation were determined for each movement cycle. The total saccadic time was obtained by subtracting the total fixation time ($\Sigma\varphi$) from the total time occupied by the given number of movement-fixation cycles. The absolute discrepancies [m − d] were computed for each movement and averaged. The relative discrepancy was obtained as ($\overline{m}$ − d), and the saccadic speed ($\overline{m}/\overline{\mu}$) was determined.

In addition to the voluntary movements, the steadiness of eyes during 5-second fixation of a point was studied. The number of involuntary movements during the middle 2 seconds of fixation and the range of movements (distance between the maximal excursion toward right and toward left) were determined. These criteria were considered only for exploratory purposes. At the magnification used for measuring the voluntary movements, the identification of small involuntary movements was difficult. The use of range of involuntary lateral movements is obviously a gross criterion, dependent on two single excursions, and the time during which the stability of fixation was observed was hardly long enough to yield a reliable score. The quantitative characteristics of the eye movements, their units, and the 'desirable' level of the scores are indicated in table 1.

The analysis of eye-movements in the above terms is limited in two respects. First, only the average values, not the variability of the different characteristics was considered. The latter would provide additional information which might be particularly valuable for using the test in conditions likely to result in occasional 'blocking' of the movements, indicative of central nervous system fatigue. Secondly, the analysis is limited to monocular behavior.

RESULTS

Consistency of the Quantitative Characteristics of Eye Movements. The data selected for the analysis of the consistency of the quantitative characteristics of eye movements were obtained in 6 successive trials, separated by 2 to 3 days. The tests were carried out under standard conditions, and involved 1) fixation

of the central point for 5 seconds and 2) shifting of the eyes from one target to the other at the maximum rate for 10 seconds. The subjects were well acquainted with the test procedure, having carried out the test more than 20 times before the present series was started.

The statistical techniques of analysis are described elsewhere (10) in detail. Briefly, three variances (mean squares) were computed for the sample of 6 scores obtained for each of the 6 subjects: *1*) The variance within days, V_{wD}, defined as the inter-individual variance (standard deviation squared), averaged for the 6 days (trials); *2*) the variance within individuals, V_{wI}, defined as the inter-trial variance, computed for each of the 6 subjects and averaged; *3*) the random variance, V_R, i.e. the variance remaining after the variation of the

TABLE 1. OPHTHALMOGRAPHIC CHARACTERISTICS OF EYE MOVEMENTS, THEIR UNITS, AND THE BIOLOGICALLY POSITIVE ('DESIRABLE') DIRECTION OF SCORES

CHARACTERISTIC	UNITS	'DESIRABLE' VALUES
Involuntary Movements		
No. movements . . .	No. during 2 sec.	Lower
Magnitude (range) . .	Degrees (visual angle)	Lower
Voluntary Movements		
Rate .	No. movement-fixation cycles/sec.	Higher
Fixation time	1/100 sec.	Lower
Movement time	1/100 sec.	Lower
Velocity of movement	Degrees per 1/100 sec.	Higher
Absolute discrepancy (true vs. traversed target distance)	Degrees	Lower
Relative discrepancy	Degrees	Lower
Extent of movement during fixation	Degrees	Lower

scores due to the differences between daily averages and individual averages was removed.

The magnitude of the random variation can be expressed with reference to the size of the inter-individual differences. In percentage form, $V_R\% = 100\ V_R$; in terms of a coefficient of consistency, $r_c = 1 - V_{wD}$. The analytical data are presented in table 2.

The fixation time, the rate of movement, and the extent of movement during fixation are very stable individual characteristics. The consistency decreases from a moderately low level obtained for the movement time to low or very low levels for the measures of the precision of the extent of the saccadic eye movements, the velocity of voluntary eye movements, the number and the magnitude of involuntary movement during 2 seconds fixation.

Changes During Consecutive Eye Movements at Submaximal Rate. In pre-

liminary trials, the maximal rate of voluntary eye movements was determined. In the present experiment, the rate was set at three-quarters of the maximal

TABLE 2. CONSISTENCY OF OPHTHALMOGRAPHIC CRITERIA OF PERFORMANCE IN A SERIES OF 6 TRIALS REPEATED ON A GROUP OF 6 SUBJECTS

	VARIANCES					
	Grand Mean	V_{wD}	V_{wI}	V_R	$\frac{100V_R}{V_{wD}}$	r_C
Involuntary Movements						
No. of movements	1.5	1.9	1.1	1.1	58	0.42
Magnitude (range)	0.38	0.43	0.29	0.26	61	0.39
Voluntary Movements						
Rate	4.22	1.78	0.03	0.03	2	0.98
Fixation time	19.3	71.2	1.1	0.9	1	0.99
Movement time	6.8	1.8	0.4	0.5	28	0.72
Velocity of movement	1.96	0.53	0.19	0.22	41	0.59
Absolute discrepancy	1.13	2.33	0.89	0.89	38	0.62
Relative discrepancy	−0.36	5.26	1.71	1.66	31	0.69
Extent of movement during fixation	0.60	0.44	0.04	0.05	11	0.89

V_{wD} = average inter-individual ('within days') variance, V_{wI} = average intra-individual ('within individuals') variance, V_R = random variance, r_C = coefficient of consistency.

TABLE 3. CHANGES IN OPHTHALMOGRAPHIC CHARACTERISTICS OF EYE MOVEMENTS

Test period = 5 minutes. Rate of movements = $\frac{3}{4}$ individual maximum rates. No. of subjects = 6. $\bar{X}_0$ = average score obtained at the start (0 to 10″ of the test period), $\bar{d}_3$ = average difference tween initial scores and those obtained at the start of the third minute of work (120″ to 130″), F_3 = value of the F-test for the statistical significance of this difference; $\bar{d}_5$ and F_5 are the differences and the F tests of the differences obtained after 5 minutes of work (300″ to 310″). The sign of the differences indicates the biological direction: + = improvement; − = deterioration.

	$\bar{X}_0$	$\bar{d}_1$	F_1	$\bar{d}_5$	F_5
Rate	2.53	+0.08	1.50	−0.10	1.25
Fixation time	36.3	+1.9	5.87	−0.7	1.72
Movement time	6.90	−1.39	3.81	−0.86	1.14
Velocity of movement	1.94	−0.37	5.66	−0.24	1.92
Absolute discrepancy	0.72	−0.43	5.13	−0.17	1.44
Relative discrepancy	(−0.24)	−0.60	18.88**	−0.24	1.81
Extent of movement during fixation	0.58	−0.38	3.86	−0.43	3.41

For paired variates at the 5% level F = 6.61, at the 1% level F = 16.26. In this and the following tables a mean change significant at the 5% level will be indicated by one asterisk, significance at the 1% level will be indicated by two asterisks following the value of F.

rate obtained during 10-second trials. A metronome was used to indicate to each individual the tempo to be followed during the 5 minute exercise period. The data are given in table 3. For the purpose of condensation only the initial

values obtained at the start of the first minute and the differences between the first and second, and the first and fifth-minute values are given.

There is no appreciable change in the number of movements. This indicates that the subjects kept up the tempo throughout the exercise period. After one minute there was some increase in the movement time but it was balanced out by the shortening of the fixation time. The absolute deviation from target distance increased somewhat and the relative deviation increased considerably, indicating that the subjects tended to 'undershoot,' i.e., to make shorter movements. After 5 minutes the picture remains qualitatively the same. There is no progressive deterioration of eye movement patterns. None of the changes observed after 5 minutes of exercise was statistically significant.

TABLE 4. SUMMARY OF AVERAGE CHANGES IN OPHTHALMOGRAPHIC CRITERIA OF PERFORMANCE UNDER CONDITIONS OF MOVING EYES AT MAXIMUM RATE FOR 4 MINUTES

No. of individual determinations = 11. $\bar{X}_0$ = average score at the start (0 to 10″); $\bar{d}$ and F represent the average differences and the value of the F test of the average differences between initial score and those obtained at the start of the second (60″ to 70″), third (120″ to 130″), and fourth (180″ to 190″) minute of eye movement exercise. The sign of the differences indicates the biological direction of the change: + = improvement; − = deterioration.

	$\bar{X}_0$	$\bar{d}_2$	F_2	$\bar{d}_3$	F_3	$\bar{d}_4$	F_4
No. movements	4.05	−1.06	23.53**	−1.12	28.21**	−1.35	22.28**
Fixation time	20.8	−7.9	75.73**	−8.2	130.98**	−10.4	98.71**
Movement time	6.23	−0.32	4.06	−0.25	0.92	−0.57	4.20
Velocity of movement	2.03	−0.16	11.11**	−0.19	9.41*	−0.23	13.04**
Absolute discrepancy	1.12	−0.10	0.47	−0.19	0.88	+0.09	0.12
Relative discrepancy	(−0.43)	−0.48	5.08	−0.34	2.07	−0.50	2.68
Extent of movement during fixation	0.75	−0.19	3.21	−0.41	8.00*	−0.41	11.68**

At 5% level of significance, F = 4.96; at 1% level of significance, F = 10.04.

Changes During Consecutive Eye Movements at Maximal Rate. The standard duration of the eye-movement test when used as a test of 'fitness' of the oculomotor apparatus was 10 seconds. In the present experiment, designed to study changes in the eye movement pattern under the strain of maximal activity, the task was continued for 4 minutes. This was close to the maximum which could be used, the watering of the eyes being the limiting factor. In one individual experiment the secretion of tears was so copious that no records could be obtained beyond the second minute. The eye movement recordings were made during the first 10 seconds of each of the 4 minutes. The data are presented in table 4.

The number of movements per second showed a very marked and progressive decrease from the first to the fourth minute of exercise. This reflects the pronounced lengthening of the fixation time. There was on the average a slight increase in the movement time and a slight decrease in the extent of

movement, indicated by the value of the relative deviation from the target distance. Although neither of these changes reached the level of statistical significance, the velocity of movement, obtained as the ratio of distance and time of movement, showed a significant decrease. The absolute deviation from the target distance was not affected. However, the amount of corrective movements during fixation increased; the change reached the 5 per cent level of statistical significance in the third minute and the 1 per cent level of significance in the fourth minute of the test period.

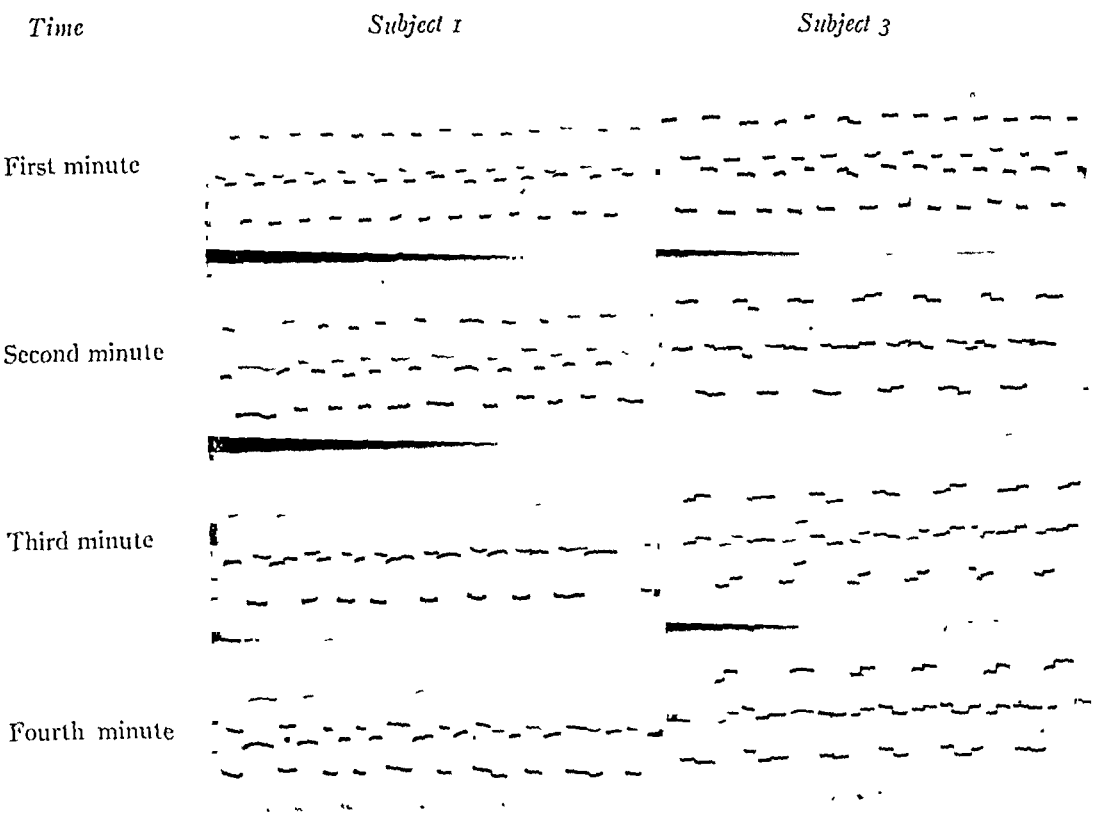

Fig. 2. SAMPLE RECORDS OF EYE MOVEMENTS (total sample time = 6 seconds) taken at the beginning of the first, second, third and fourth minute of continued eye-movement activity carried out at a maximal rate.

Six-second samples of eye movement patterns obtained for 2 subjects at the start of the 1st, 2nd, 3rd, and 4th minute of the exercise period are presented in figure 2.

Changes Resulting from Strenuous Inspection Work. The two stresses discussed above, i.e. repetitive eye-movements carried out at a sub-maximal but high and regulated rate and at the maximal rate, may be useful for abstract laboratory research. However, the value of the ophthalmograph for realistic investigations on fatigue, especially industrial fatigue, depends on the sensitivity of the ophthalmographic criteria of oculomotor performance to the physiological strain imposed by prolonged visual work.

As an illustration, changes in eye-movement patterns will be reported which were observed after 2 hours of uninterrupted, strenuous visual work. Voluntary eye movements, carried out at maximal speed for 10 seconds, were recorded before and after the work. The work task involved recognition of very fine details (letters 3.5 points in size) which passed through a narrow vertical slit. It reproduced in miniature the essential features of an industrial inspection operation of objects transported on a conveyor. The technical details and the method of evaluating the work performance are described elsewhere (11). As far as the eye movements are concerned it may be noted that the subjects had to scan the slit over its whole height (3 in.). The lateral eye movements were limited by the narrow width of the slit ($\frac{1}{8}$ in.).

TABLE 5 CHANGES IN OPHTHALMOGRAPHICALLY RECORDED EYE MOVEMENTS AFTER 2 HOURS OF VERY HARD VISUAL WORK (2 F.C). NO. SUBJECTS = 6

	BEFORE WORK		AFTER WORK		MEAN DIFFERENCE	F-TEST
	Mean	S D	Mean	S D		
Involuntary movements						
No. of movements	1.2	0.8	3.2	2.7	−2.0	2.73
Magnitude (range)	0.48	0.29	0.99	0.86	−0.51	2.58
Voluntary movements						
Rate	4 4	1.6	3 6	1.0	−0.8	9.30[1]
Fixation time	18.2	8.4	21.8	7.6	−3.6	23.87[2]
Movement time	6.7	1.3	7 3	1 0	−0.6	4.15
Velocity of movement	1 92	0 46	1.75	0 26	−0.17	2.55
Absolute discrepancy	1.44	1 00	1.37	0.72	+0 07	0.18
Relative discrepancy .	(−0 82)	1.44	−0 72	1 11	+0.17	1.00
Extent of movement during fixation	0 55	0 22	0.82	0 34	−0.27	11.51[1]

[1] Using paired variates, the value of F at the 5% level of significance = 6.61.[2] At 1% level of significance, F = 16.26

The signs of the differences indicate the 'biological' direction of the change: deterioration (−) or improvement (+).

After 2 hours of visual work at 2 foot-candles the most consistent changes were the lengthening of the fixation phase and increase in the magnitude of the 'involuntary' eye movements during fixation (table 5). There was a small increase in the duration of the movement phase and decrease in the velocity of the saccadic eye movements. However, the decrement in the rate of eye-movements was due primarily to the increase in the duration of the fixation phase. The accuracy of eye movements measured by the deviation from the target distance was not affected. There was some increase in the number and the extent (range) of involuntary movements observed during prolonged fixation before the start of the eye movement exercise.

Statistically significant changes were obtained also when eye movement

patterns were studied before and after 2 hours of inspection work carried out at higher foot-candle levels (12). A decrement in the number of eye movement cycles per second was present at all levels of illumination, from 5 to 300 F.C. Most of the other eye movement characteristics changed also in the direction of deterioration but the changes did not reach, except for lengthening of the movement and the fixation phase, a level of statistical significance.

DISCUSSION

Eye Movement Patterns as Measures of Neuromuscular Fitness and Fatigue. In the course of investigations on the effects of nutritional deficiencies we became interested in quantitative analysis of eye movements as means for characterizing one aspect of neuromuscular function in man. The standard test battery (13) contained measures of speed of movements (two-plate tapping, complex reaction-time), of coordination (repetitive skilled movements, pattern tracing), and strength (hand grip and back lift). Because of the fine coordination of nervous impulses required for the execution of eye movements, a possibility of its disturbance under strain made the eye movements a promising criterion of fitness and fatigue. The fact that the complex performance could be analyzed in quantitative terms was an added incentive.

The test of voluntary eye movements can be arranged in such a way that it will serve as a test of performance capacity, defined as the maximal performance obtainable; when the activity is continued, the amount of deterioration can serve as an index of fatigability, the reciprocal of endurance. It should be noted that when the eye-movement test is used as a test of endurance, the activity may be carried either at the highest level of effort or at a sub-maximal, regulated tempo. In the latter case only the pattern of eye movements, in the former case also the rate can be used as the criterion of performance.

It has been a rather general experience that changes in fitness due to illness as well as the experimentally induced alterations in fitness may be demonstrable at times under conditions of superimposed stress while they are latent in rest or under optimal conditions of performance (14). The changes in eye-movement patterns, measured at successive intervals of a continued activity, may be a more sensitive criterion than the scores obtained during a very short period in which the factor of endurance does not enter.

Components of the Eye Movement Pattern. Although both eyes were used in the eye-movement test, the tracings were analyzed for only one eye. On inspection, the movements of the two eyes were carried out with a surprising degree of accuracy (parallelism) even at times when other aspects of performance showed evidence of deterioration. This is not to say that in fatigued eyes the disturbance of fine binocular coordination might not be present. For quantitative investigations of this problem a greater magnification of the excursions of the eyes would be required than was used in the present series.

The two basic 'dimensions' of eye movements are the duration and the magnitude of lateral displacement. The time of an eye-movement cycle was broken down into the movement time and the fixation time. The spatial aspects of the eye movement patterns were resolved into the magnitude of the saccadic movement and the magnitude of the 'corrective' movements during fixation. An absolute and a relative measure of imprecision of saccadic movements in target fixation was obtained. The time of movement and its distance yield a derived score, the (average) velocity of the movements.

In the rapid muscular movements, carried out back and forth between two positions, one may differentiate usually three phases: *1*) acceleration, *2*) uniform (maximal) velocity and *3*) deceleration. The three phases were observed by Dodge as early as 1903 (15) but as far as we are aware no quantitative analysis of the changes in velocity was carried out either by Dodge or by other investigators. It would be valuable to study not only the overall (average) velocity but also such characteristics as the maximum speed and the pattern of acceleration and deceleration of eye movements, and their changes in fatigue. This would require a much higher speed of the film allowing for an increase in the precision of quantitative analysis of the movements.

Reliability of Eye Movement Measures. As far as we are aware there are no data in the literature on the consistency of the quantitative characteristics of voluntary eye movements. Several of the criteria of voluntary eye movements used in the present study have high (extent of corrective movements during fixation) to very high (fixation time, rate of movement) coefficients of consistency. In fact, these features of the eye movement patterns are more stable than many a feature of the electrocardiogram (16). With reference to the consistency, the eye movement characteristics compare favorably with the routine ophthalmological (17) and other visual tests (18), studied with reference to consistency under similar conditions.

It is realized that the reliabilities computed on the basis of 6 subjects are only tentative and that all coefficients should be corrected to the scatter of values in the population of 'normal young men' from which the subjects were drawn (19). For this reason it is advantageous, though somewhat space-consuming, to report not only the coefficients of consistency but also the basic variances from which they are derived.

Observed Changes in Voluntary Eye Movement Patterns under Stress. In the pioneer study by Dodge (20) the subjects moved their eyes horizontally through an arc of 60° in rapid succession. The beam of light, interrupted in such a way that each dot represented an interval of 8 msec., was reflected from the cornea onto a moving photographic plate. The continued eye movement activity modeled after ergograph performance resulted in some decrease of the speed of movement, decrease in the accuracy of fixation, and in irregularity of the line of movement, due to the interference of vertical movements. These changes

were noticeable on inspection of the records, one of which was published in Dodge's paper. No attempt was made at that time to characterize the changes in strictly quantitative terms. Our test task, except in one series, was identical with that of Dodge, in contrast to most of the later work in which the ocular movements were carried at a sub-maximal, imposed tempo (21–24), with the speed of saccadic movements used as the primary criterion of performance.

It was our general experience that the duration of the fixation interval showed more pronounced fatigue changes than the speed of the eye movements. The latter was only slightly less than under standard normal conditions and in a large number of experimental series the change in speed did not reach the level of statistical significance. This indicates that the muscular performance capacity was largely unaltered. In terms of the 'site' of the fatigue changes, the effects were central rather than peripheral (muscular).

Under conditions of reading the duration of fixation is predominantly a function of the central nervous system; e.g. it is well known that the fixation time increases with the intellective difficulty of the text (cf. fixation in reading fiction and in studying algebra). In our task the fixation time was determined by at least three factors: *1*) an adequate exposure of the retina (perception time); *2*) overcoming the inertia of the oculomotor system; and *3*) delay in the initiation of a contraction of the antagonist and relaxation in the agonist muscles.

Under conditions of strain there is no change in the second factor (which is small in any case) and, most probably, the perception time is not affected either. The observed increase in the fixation time is probably due to the third factor, not to muscular fatigue. Similarly, the increase in corrective movements during fixation reflects disturbance of coordination of the nervous impulses.

The arrest of motion at the turning points is a feature common to all types of work which involve repetitive (to-and-fro) movements. It is of interest, therefore, to compare the lengthening of the fixation time observed in repetitive eye movements with the pauses occurring in moving loads (25). Several different loads were compared, a higher load representing a higher 'strain.' In general, the increase of the load produced a prolongation of the pauses between the reversed movements. However, these pauses between the reversed movements and the fixation times in eye movements are not functionally identical even though they have common elements. In both cases the pause is due in part to the shift of the innervation from agonists to antagonists. The overcoming of inertia of the system is an important component in moving loads. In eye movements a part of the fixation time is utilized for perception, which is an essential element in the task, while in moving loads the pauses represent unproductive time. Actually, the time is not fully 'unproductive' because a partial recovery takes place during the pause, contributing to the maintenance of work capacity.

The lengthening of fixation may at times appear as 'blocking' of the eye

movements. The effect of blocking was studied most intensively by Bills (26). It is present in 'mental' tasks, such as naming colors of a series of squares painted in a limited number of hues, or substituting letters for digits according to a key, but also in other types of work involving a rapid repetition of a limited number of responses or the same response, such as tapping. 'Blocking' is considered as a symptom of the fatigue of the central nervous system. Whereas the muscular fatigue manifests itself as a progressive decrease in the response of a repeatedly stimulated muscle, in blocking there is *no* response for a certain time period—a fraction of a second—in the eye movements. This condition is obtained in muscular fatigue only in the terminal phase of exhaustion. In blocking, the performance between 'blocks' is little affected.

In the series of experiments reported in this paper the most pronounced changes in the eye movement patterns took place during the 4 minute, maximal-rate experiment. However, even there the point of 'exhaustion' was not reached. Two mechanisms contributed to this: *1*) 'blocking' of eye movements served as means for enforcing involuntary rests; *2*) lacrimation, which may be interpreted as a result of the spread of innervation to other effectors, made impossible recording of the eye movements beyond 4 or 5 minutes.

The relative sensitivity of oculomotor characteristics to the stress of severe visual work as compared with other visual functions was discussed in another publication (27).

SUMMARY

The consistency of 9 eye movement characteristics, measured in photographic records obtained for each of 6 normal young men on 6 occasions, varied from very high (fixation time, rate of movements), high (extent of corrective movements during fixation), moderate (movement time) to low and very low.

In the course of a 'stress' consisting in shifting the line of regard through about 14° at a sub-maximal rate for 5 minutes, all eye movement characteristics changed in the direction of deterioration but none of the changes reached the level of statistical significance. In a more severe stress which involved eye movements carried out at the maximal attainable rate for 4 minutes, the rate of movements declined, due primarily to a marked increase in the fixation time; the velocity of movements decreased and the extent of corrective movements during fixation increased. In the third stress situation consisting of 2 hours of hard inspection work at a very inadequate illumination, the fixation time and the corrective movements increased, while the rate of movements decreased. The changes were much less pronounced than in the preceding experiment. The lengthening of the fixation time, reaching at times the magnitude of a 'mental block,' as well as the increase in the corrective movements during fixation were interpreted as fatigue phenomena localized in the central nervous system. Muscular fatigue was much less evident or was absent.

It is a pleasure to thank Dr. Ancel Keys and Dr. Ernst Simonson for their help and encouragement at all stages of research reported in this paper. The possibility of studying eye movements as a measure of neuromuscular coordination in experimentally induced nutritional 'stresses' was suggested by Dr. Russel M. Wilder. This provided the initial stimulus for the development of the present technic.

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Volume Changes in Forearm and Hand Following Release of Obstruction to Venous Return

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WHEN THE PRESSURE in a sphygmomanometer cuff which has been obstructing the venous return from the forearm is released, the limb volume returns to normal in three stages. There is firstly a rapid primary decrement in volume (hereafter referred to as the 'P.D.'); secondly an occasional small increase in volume, as shown by a 'Hump' on the volume record; and finally a phase of gradual reduction (or secondary decrement 'S.D.') as the limb volume returns to normal. Typical tracings are shown in figure 1. These three stages have been described by Lewis and Grant (1). It was considered that a further examination of these phenomena with a view to elucidating the mechanisms involved would be of interest. The second and third phases, i.e. the Hump and the final phase of recovery (S.D.), have been examined by Lewis and Grant; but not so much attention has been paid to the first phase of sudden reduction in limb volume (P.D.).

METHODS

The plethysmograph was of a 'water' type. The outer jacket contained enough water to make temperature changes negligible. Volume changes were recorded by means of a float writing on smoked paper. The venous return from the limb was obstructed by means of a sphygmomanometer cuff. The latter was connected to a 10-liter reservoir by means of which the pressure could be raised to that required, in 3 to 5 seconds. The opening of a large bore tap connected to a cuff allowed an immediate release of the pressure. The range of the pressures used was 30 to 70 mm. Hg.

The plethysmograph was designed so that the arm was held in a vertical and dependent position by the side of the sitting subject. This position was considered to be important. It is suggested that if the arm were held in a horizontal position the reduction of the limb volume following the release of the pressure in the obstructing cuff would be due to two factors: 1) the ejection of blood from the limb vessels by virtue of their inherent tone and elasticity and

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2) the drainage of blood from the limb vessels due to gravity. The adoption of the dependent vertical position was an attempt to eliminate this second factor and to record only the reduction in limb volume due to the recovery of the vessels by virtue of their tone. With the limb in the dependent vertical position the vessels will not be drained by gravity but will remain 'filled' after the release of the obstruction. The adoption of this position for the limb produced a clearer separation of the three phases. Lewis and Grant placed the arm in a horizontal position.

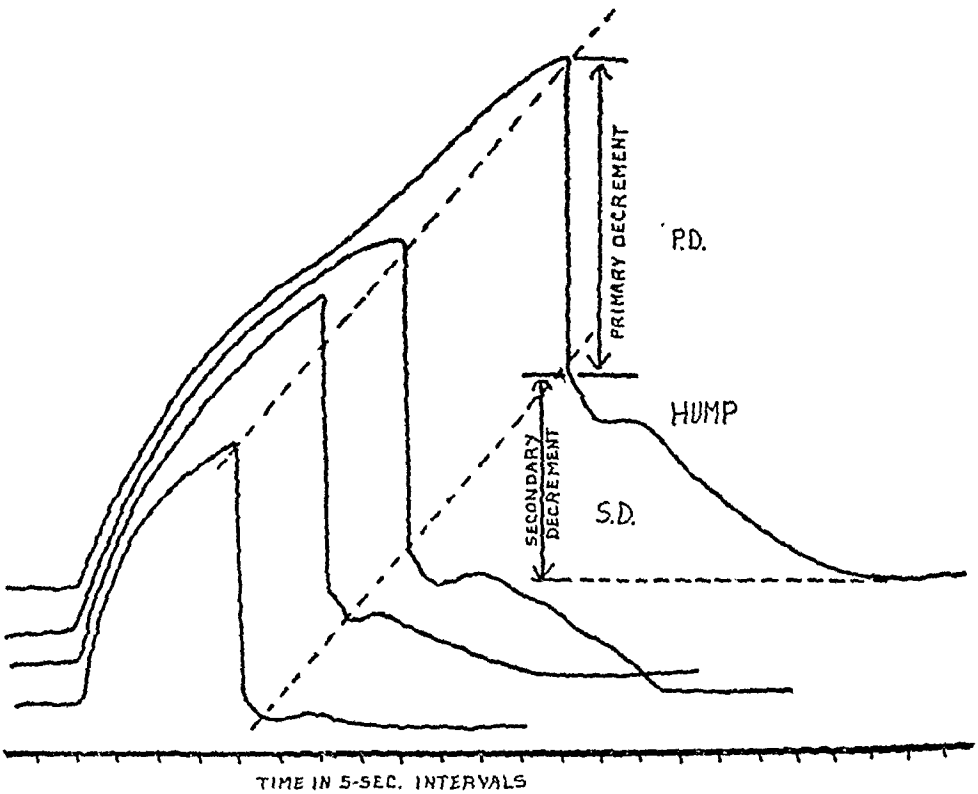

Fig. 1. FOUR CONSECUTIVE TRACINGS superimposed showing the effect of duration of obstruction of venous return on decrements in limb volume. Note the 3 phases that follow release of the tourniquet: *a*) the rapid primary decrement in limb volume, P.D.; *b*) the Hump; *c*) the secondary decrement, S.D.

RESULTS

The series included over one hundred experiments on 13 subjects.

Influence of Duration of Obstruction of Venous Return on P.D. and S.D. As the length of the period of obstruction is increased the P.D. soon reaches a maximum after which no further significant increase in its size occurs with longer applications of the obstruction. The S.D. behaves in a different manner. Long after the P.D. has reached its maximal value the S.D. continues to increase and does not reach a maximal value within the times of applications of the obstruction adopted here (viz. up to 10 minutes). These points are illustrated in figures 1 and 2.

Ratio of P.D. to S.D. in Hand and Forearm. This was examined in order to determine the respective parts played by the superficial and deep vessels (see DISCUSSION). No significant difference between the two ratios was observed.

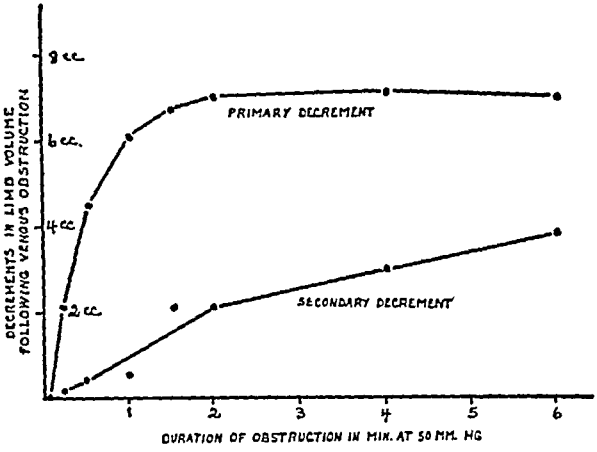

Fig. 2. INFLUENCE OF DURATION OF OBSTRUCTION of venous return on decrements in limb volume. Each point represents the average of 12 readings.

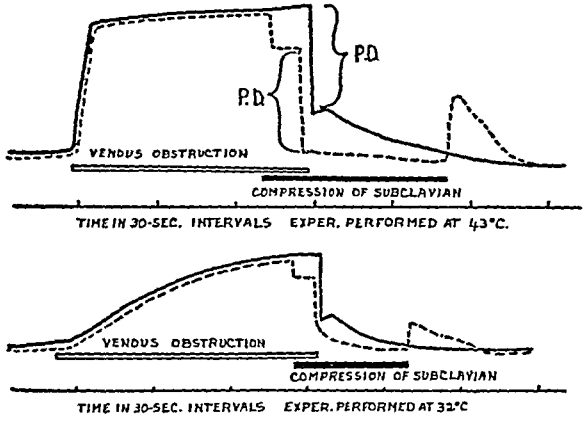

Fig. 3. DIAGRAMS, DRAWN FROM TRACINGS, showing influence of compression of subclavian artery on the P.D. in the same subject at temperatures of 43° C. and at 32° C.

Effect of Compressing Subclavian Artery. This was accomplished by digital compression of the subclavian artery against the first rib behind the clavicle. The results of such a procedure are shown diagrammatically in figure 3. As the artery is compressed there is a fall in limb volume, and when the compression is removed, there is a marked increase in limb volume. Unless these changes in limb volume were observed no measurements were made. The P.D. and S. D. are recorded during the arterial compression by releasing the venous ob-

struction, when it can be observed that the size of the P.D. is unaltered, but that the Hump is abolished. The abolition of the Hump means that it is not always possible to clearly define the P.D. and S.D.

During any one experimental session the S.D. was more variable than the P.D. Both P.D. and S.D. showed a tendency to increase by 10 per cent to 30 per cent in the course of a session. To obviate this effect, the order in which the venous obstructing pressures were applied was first in an increasing order, then in a decreasing order; the results for each pressure were then averaged.

A typical experiment is recorded in table 1. The order of the readings is given and it can be seen that recordings of the effect of compression of the subclavian artery on the P.D. were made alternately with control readings.

TABLE 1

ORDER OF READINGS	VENOUS OBSTRUCTING PRESSURE IN MM. Hg	SIZE OF P.D. IN MM.	
		With compression of subclavian artery	Control
1	30	8	
2	30		12
3	40	19	
4	40		20
5	50	26	
6	50		25
7	60	35	
8	60		31
9	60	32	
10	60		35
11	50	30	
12	50		29
13	40	24	
14	40		22
15	30	14	
16	30		14

The length of the periods of venous obstruction was determined by the time that it took the limb volume to reach a plateau. Periods of 2 to 3 minutes were found to be adequate. Between each obstruction a period of 2 to 3 minutes was allowed for the return of the limb volume to normal.

In figure 4 are distribution diagrams of four experimental sessions under similar conditions where the effect of compression of the subclavian artery on the P.D. was being examined. It will be seen that there is no significant difference between the averages for the controls and the averages where the subclavian artery was compressed, although the scatter may be greater in the latter group.

Time Required to Complete the P.D. At normal temperatures (32°C.), this usually occurred within two seconds.

Influence of Different Temperatures and Pressures. An example of the effect on the P.D. of varying both the temperature in the plethysmograph and the obstructing pressure is shown in figure 5.

The pattern of the changes in limb volume *following* the release of *digital* obstruction of the *subcutaneous* veins was compared with that following the

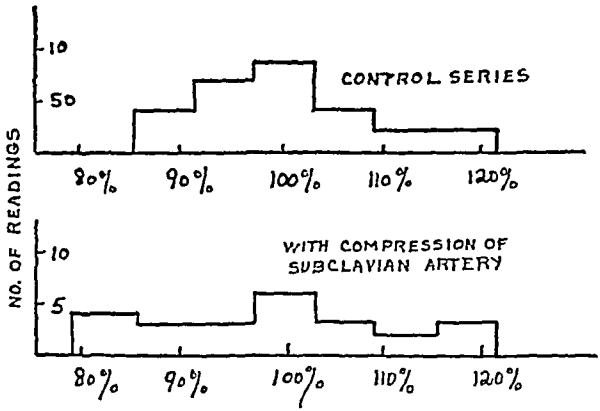

Fig. 4. DISTRIBUTION DIAGRAMS of the P.D. with and without compression of the subclavian artery. In each group of readings the results are expressed as a percentage of the average of the readings of the control series.

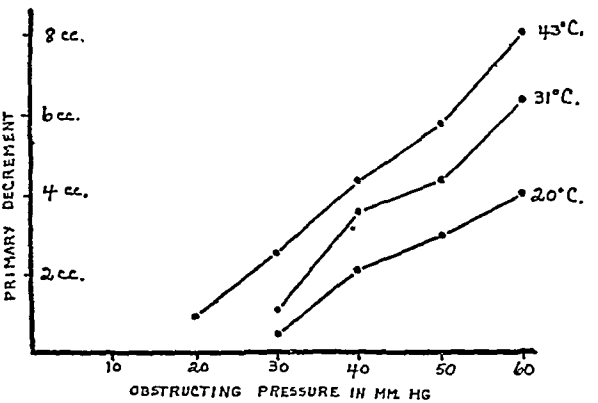

Fig. 5. A SINGLE EXPERIMENT showing influence of temperature and pressure on primary decrement in limb volume.

release of a sphygmomanometer cuff which compressed both the superficial and deep veins. A subject with prominent superficial veins was chosen, and his cephalic and basilic veins were occluded at the same time by light digital pressure. The pattern of the changes in limb volumes was similar to that following the release of pressure in a sphygmomanometer cuff.

Correlations have been evaluated between the P.D. or S.D. and the rate of increase of limb volume at the beginning and towards the end of the period

of venous obstruction. The only statistically significant correlation, which is positive, is that between the S.D. and the rate of volume increase during the latter part of the obstruction period, provided that the cuff pressure is not greater than 40 mm. Hg.

DISCUSSION

Under certain conditions (notably at temperatures of approximately 40°C.), when an obstruction to the venous return is applied to the arm the *filling* curve or *increase* in limb volume may show two distinct phases. First, there is an abrupt increase in limb volume. This is generally accepted as being due to the filling of the veins which may be seen to increase in size. A second phase of more gradual increase in volume follows which is probably due to the rise of pressure in and the distension of the smaller vessels such as the venules, capillaries, and arterioles. This secondary rise in volume is not likely to be due to the accumulation of tissue fluid which is a more gradual phenomenon.

The phases of the recovery of the vessels and the *decrease* in limb volume following the *release* of an obstructing cuff follow a similar pattern, but can be more clearly defined and separated, because of the rapid formation of the P.D. and the presence of an angle (and Hump) dividing the P.D. from the S.D. It is likely that the first rapid reduction in volume P.D. is due to the recovery of the large veins from the distending force caused by the obstructing cuff, and the secondary more gradual decline in volume (S.D.) is due to the recovery of the smaller vessels.

It is suggested that the application of the obstruction soon causes a maximal distension of the large veins (thus forming the P.D.) but that the smaller vessels do not reach a maximum during this period but continue to be distended and increase in size (forming the S.D.). In order to examine these suggestions, the following questions were examined:

a) *To what extent does an arterial factor enter into the formation of the P.D.?* This was examined by occluding the subclavian artery as described above. As this procedure had no significant effect on the size of the P.D., it suggests that an arterial element does not play a significant part in the formation of the P.D.

b) *To what extent do the smaller vessels such as the capillaries, venules and arterioles enter into the formation of the P.D.?* This is a difficult question to answer. In order to examine this point the hand was immersed in water at 43°C. and a tourniquet completely occluding the limb circulation was applied. Very soon the limb became cyanotic. When the tourniquet was released more than two seconds elapsed before an observable change in skin color was apparent, and consequently before a significant blood flow had passed through the smaller skin vessels. At the lower normal temperature (water bath 32°C.) the P.D. was completed within two seconds, and thus this probably occurred before any significant flow of blood passed from the smaller vessels.

c) Is it possible that the P.D. represents the drainage of the superficial vessels, and the S.D. the drainage of the deeper vessels, or vice versa? It might be argued that when a cuff obstructing the venous return is applied it would first distend the superficial vessels and later those more deeply placed, and that on removal of the obstruction one set might empty before the other and consequently account for the two decrements of limb volume that are observed. To examine this point, the ratio of the P.D. to S.D. in the hand and forearm were compared. (In the hand there is a larger ratio of superficial to deep vessels than in the forearm.) As the ratios of the P.D. to the S.D. in the two instances were not significantly different it is considered that the answer to the above question is in the negative. This is supported by the observation that where superficial veins were digitally compressed the usual pattern of reduction in limb volume was observed with the formation of both the P.D. and the S.D.

From these observations it is suggested that the major factor entering into the formation of this primary decrement in limb volume (P.D.) is the rapid recovery of the large veins from the distending force. If this can be accepted a curve representing an index of venous distensibility might be obtained by relating the size of the P.D. to the distending pressure. Such a curve is shown in figure 5. The influence of temperature on the P.D. is shown in figure 5. It is well known that cold increases the tone of the veins. The P.D. under these conditions being markedly reduced. Capps (2) has examined the possibility of determining indirectly the tone of the vessels in the hand. He made use of the filling curve, but no attempt was made to distinguish the vessels involved.

SUMMARY

Observations were made on the changes that occur in the volume of the forearm and hand following the release of an obstruction to the venous return. The presence of three phases has been confirmed: *a*) a rapid primary decrement (P.D.) followed occasionally by *b*) an increase in volume (Hump), and finally *c*) a secondary decrement (S.D.) as the limb volume gradually returned to normal.

It is suggested that the primary decrement in limb volume (P.D.) is largely venous in origin and is probably due to the rapid initial ejection of blood from the limb as the large veins recover their normal size and calibre. An index of venous distensibility is suggested which might provide a means of indirectly measuring venous tone.

Grateful acknowledgement is made for the grant from the King's College, (Newcastle) Research Fund, and for the technical assistance of Mr. R. A. Spires.

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Industrial Efficiency as Affected by Food Intake During Mid-morning and Mid-afternoon Rest Periods[1]

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RECOGNITION of the strategic importance of maximum productivity during the war by industrial workers led to the publication of a brochure under governmental auspices on the relationship of food and nutrition to industrial efficiency (1). In this report which consists largely of a commentary on the feeding practices in industrial plants, pointed criticisms were made on the nutritional status of industrial workers, the kind of meals served in the plants, and the selections made by the industrial workers from the rolling carts that are customarily sent through many plants in mid-morning and mid-afternoon.

The premise that a good state of nutrition favors work productivity seems hardly open to question. Equally acceptable is the assertion that the meals served in a plant should be highly nutritious. But the assumption made in this report that the industrial worker requires a substantial amount of food at the mid-morning and mid-afternoon rest periods in order to maintain a high degree of efficiency cannot be accepted without more convincing evidence.

The more or less common inclination to stop work in mid-morning and mid-afternoon and to partake of food or a beverage at those times raises a fundamental question. Is it that the energy reserves of the worker have been reduced to the point where the organism demands food or is it for some psychological reason, such as the desire for a restful change from monotony and for the refreshment that is derived from eating appetizing food or from drinking a pleasing beverage?

Some investigators are led to believe from their experimental observations that several hours after a meal there occurs a fall in the blood sugar and carbohydrate reserves and a consequent feeling of tiredness, disinclination to work and a lowering of work productivity (2, 3). In our opinion the available evidence is not sufficient to warrant a universal application of this principle. For this reason the present study was undertaken in a different industry than that studied by other investigators, to determine whether the efficiency of the

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[1] The expense of this investigation was defrayed by a grant-in-aid from the Sugar Research Foundation.

workers might be related to the kind and amount of food eaten in the mid-morning and mid-afternoon rest periods.

PROCEDURE

The experiments were conducted in the sewing room of a large cotton bag factory. The subjects were all women who worked at top speed continuously throughout the working hours of the day sewing bags on electrically driven sewing machines. They had volunteered to serve as subjects after they had been told in convocation that the investigators were studying certain aspects of nutritional problems and that the food would be served to them free of charge. In order to avoid the possibility of any suggestion that might affect the work output, the precise nature of the experiment was not revealed. Excellent cooperation was obtained both from the managerial personnel and from the employees who served as subjects.

In a study of this nature it is essential that there be a wage incentive for maximum exertion on the part of the employees. This requirement was met in this particular factory inasmuch as it operated on the piece work system, each worker being paid in accordance with her production.

Work was begun in the morning and concluded in the late afternoon at exactly the same time each day. In the morning the electric current was turned off at 9:30 and again in the afternoon at 2:30, stopping all the machines for fifteen minutes while refreshments were served. Toward the end of this period a signal was given in ample time to allow the workers to be at their machines ready to resume work when the current was turned on again.

An hourly count of the number of each kind of bags sewed by each subject was made and recorded by employees trained in this procedure. A supply of bags was available at all times at each machine so that sewing could be continued uninterrupted. When one lot of bags was completed, the next lot frequently was of a different size and texture. Obviously the work output, therefore, could not be determined by the sole criterion of the number of bags sewed. In this factory which had a record of many years' successful operation, a careful study and evaluation had been made on a comparative basis of the relative time required for sewing different kinds of bags. This evaluation was expressed in terms of standard hourly production. If, for example, the standard hourly production of one kind of bag was 800 and that of another 500, a worker sewing 800 of the first kind of bag in one hour and 500 of the second kind in another hour would have a standard hourly production of 100 per cent for each hour. The standard hourly production would also have been 100 per cent if the worker had shifted from one kind of bag to another during the hour and had sewed 400 of the first kind and 250 of the second kind. The standard hourly production during the experiment was accordingly determined from the record

obtained on the number and kind of bags sewed during each hourly period. All production data reported in this paper are given in terms of standard hourly production.

In view of the limited objective of this experiment it was not considered necessary to determine the blood sugar levels at the different hours throughout the day.

For three consecutive weeks one of the following refreshments was served each day during the mid-morning and mid-afternoon rest periods: *1*) large frankfurter, one bun, generous helping of potato chips and one bottle of a soft drink; *2*) slice of pound cake (approximately 2 ounces), one large banana, ½ pint milk; *3*) one bar Hershey's milk chocolate; *4*) a soft drink only. These various refreshments will be resferred to as *1*, *2*, *3* and *4*, respectively. The order of serving the refreshments on successive days was different each week. One day in each of two successive weeks no food at all was eaten during the rest periods.

It was estimated that the caloric yield of the four refreshments was approximately 650, 350, 150 and 80 calories, respectively. For the purposes of this experiment it was deemed sufficient to have refreshments of widely varying caloric content and composition without making exact determinations thereof. A rough estimation indicates that the four different refreshments contained approximately 63, 70, 54, and 100 per cent carbohydrate, respectively; 13, 15, 9 and 0 per cent protein; and 24, 15, 37 and 0 per cent fat.

RESULTS

Thirty-two seamstresses served as volunteer subjects. If all of them had reported for work each day of the week there would have been available complete data on 96 working days with each type of refreshment. It was soon observed that hardly a day passed without one or more absences. Since there was an appreciable difference in hourly production by the various employees, it was decided to use the data only when an employee worked each day of the week. This was done so as to present only those data that were strictly comparable under the different conditions of the experiment. However, it is worthy of note that further calculations showed that inclusion of all the data would have introduced only a very slight and insignificant difference in the averages.

The average hourly production of the seamstresses during the pre- and post-refreshment periods is presented in table 1. Each value in the table is an average obtained from 52 work days. It is apparent from these data that there were only slight differences in production on the days when different kinds and amounts of food were served during the mid-morning and mid-afternoon rest periods. These differences were not statistically significant. This was confirmed by an analysis of the wages received by the workers on the days when different refreshments were served. The differences ranged from one-tenth of a cent to

one and a half cents per hour. The maximum difference was considerably less than 3 per cent of the highest average hourly wage (group average) during the experiment. The critical ratio of the largest difference in hourly work output after the various refreshments, as shown in table 1, was 1.2. Lower critical ratios were obtained for the other differences.

TABLE 1 HOURLY PRODUCTION OF SEAMSTRESSES ON DAYS ON WHICH DIFFERENT REFRESHMENTS WERE SERVED DURING MID-MORNING AND MID-AFTERNOON REST PERIODS[1]

REFRESHMENT	PERCENTAGE OF STANDARD HOURLY PRODUCTION					
	Morning			Afternoon		
	7 30–9 30	Refreshment Served	9 45–11 30	12 00–2 00	Refreshment Served	2 15–4 30
1. Approx. 650 Cal	123		138	125		135
2. Approx 300 Cal	123		136	122		131
3 Approx 150 Cal	124		133	123		135
4 80 Cal	122		134	123		133

[1] Each value in the table is an average of 52 work days

DISCUSSION

These experiments show that in this type of industrial work, efficiency is not affected by the amount or kind of food eaten during the mid-morning and mid-afternoon rest periods. Without supplementation the energy reserves derived from the usual meals appear to be sufficient for the day's work, even though it is of a somewhat exacting nature. As stated previously, the subjects in this experiment worked continuously and at top speed.

However, it should not be concluded from these experiments that refreshment for the workers during the morning and afternoon rest periods might be regarded as a matter of indifference. On the contrary, our observations lead us to the conviction that from the point of view of industrial efficiency, such refreshment should be made accessible to the workers; furthermore, that their tastes and desires should be taken into account and that they should be allowed freedom of choice.

This conclusion is based on several considerations. On the two days of the experiment when no food was eaten during the rest periods there was no impairment in work output, probably because of the generous cooperation on the part of the workers. However, it became obvious that the workers were not pleased over being allowed no food or a favorite beverage. The objections that were voiced became so pronounced that we considered it expedient at the end of the second week to abandon our original plan of conducting the experiment one day in each of three consecutive weeks without refreshments.

Another consideration is the satisfied state of mind created in the worker by providing him with food and beverages that gratify his taste. It has been

observed by other investigators (4, 5) that the productivity of industrial workers may be adversely affected by unfavorable psychological states, as for example, those occasioned by domestic problems, economic anxiety, emotional disturbances, social frustrations and frictional management-employee relationships. It is not unreasonable to suppose that a resentful frame of mind might be engendered either by denying the workers access to food and beverages or by an attempt toward regimentation in the matter of what they should eat or drink.

It will be observed in table 1 that there was a higher level of productivity in the second half of the morning and afternoon as compared with the preceding periods. The increased output, it appears, could not be accounted for by the brief rest period and the food eaten at this time because prior to the first hour of the morning and afternoon when the output was lowest, the workers had a longer period of rest and an appreciable amount of food. The same increase in production was observed in late morning and late afternoon on those days when no food was eaten during the rest period. These observations may be taken to indicate that food intake and the rested state of the organism are not the sole determining factors in work productivity.

SUMMARY

The industrial efficiency of seamstresses in a large cotton bag factory was not affected by the kind and amount of food eaten during the mid-morning and mid-afternoon rest periods. On the basis of this observation and other considerations it is concluded that from the point of view of industrial efficiency workers should be allowed a reasonable freedom of choice of what they eat and drink during the rest periods.

ADDENDUM

Although it is not pertinent to the primary objective of this investigation, it may be permissible to record an interesting observation that there were marked differences in the industrial efficiency of different workers, and that an analysis of the company's records of all the employees revealed that there was no relationship between length of service and efficiency. This would suggest that the difference in productivity may have been related to innate neurophysiological aptitudes for this particular kind of work. When the average hourly wages of the individual workers for a period of nine consecutive weeks were arranged in deciles, the resultant figure resembled a normal distribution curve. Although the evidence is not conclusive, it is highly suggestive that the type of work which we were studying is executed by certain anatomico-physiological mechanisms which are distributed among the population somewhat like body weight, height, intelligence, reaction time etc. It would seem to be to the advantage of industry to explore this possibility, for obviously it would be highly profitable if tests could be devised for selecting employees with the highest productive potentialities. As the overhead and maintenance cost of identical machines is the same, it is apparent that the variable affecting the yield on capital investment is the efficiency of the individual operators.

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Hemoglobin Concentration and Physical Fitness

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EFFICIENT PERFORMANCE of muscular exercise demands an adequate supply of oxygen to the tissues and, in conformity with this, we have already demonstrated that the ability to perform severe exercise is correlated significantly with the subject's vital capacity (1). Since hemoglobin is the oxygen-carrier between the lungs and the active tissues, it is of interest to see if the hemoglobin concentration of the blood is correlated significantly with the various aspects of physical fitness. Spealman *et al.* (2) could find no indication of a correlation between hemoglobin concentration and exercise performance at high environmental temperatures, but Karpovich and Millman (3) found a reduction in performance for some days after the subjects had acted as blood donors.

METHODS

The hemoglobin concentration was measured simply by Sahli's method. The exercise tests performed by the subjects were a moderate exercise test, i.e. the Harvard Step Test (4); a severe exercise test, i.e. the Endurance Step Test (5); a prolonged moderate exercise test (6); a strength test (5) and a speed test. Male and female Ceylonese subjects aged 10 to 20 inclusive performed the tests.

Wet and dry bulb and globe thermometer readings were recorded; the mode of the temperature was 84.6° F. and the mode of the relative humidity was 76.2%.

Coefficients of correlation between the hemoglobin concentration and the ability to perform the various types of physical exercise have been calculated.

RESULTS

Hemoglobin Concentration and Speed of Running. Forty-six schoolboys (aged 14–20 years) were timed while running competitively a distance of 100 yards. The coefficient of correlation between these times and the hemoglobin concentrations for this group has a value of -0.3602, which is significant at the level of $P = 0.02$. Since speed of movement is inversely proportional to the time taken to run 100 yards, we can conclude that the greater the hemoglobin concentration the faster the speed of running.

The range of hemoglobin concentrations for the group was 11.4 to 18.7

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gm/100 cc. blood, with a mean of 15.1 ± 0.228; the range of times was 16.2 to 10.3 seconds, with a mean of 13.8 ± 0.255.

Hemoglobin Concentration and Response to Moderate Exercise. The moderate exercise consisted of the 5-minute Harvard Step Test and, from the post-exercise pulse rates, the fitness index pulse for each subject was calculated. The test was performed by 200 male and female subjects, aged 10 to 20 years inclusive. Hemoglobin estimations (Sahli) were made before exercising. The coefficient of correlation between the fitness index (pulse) and the hemoglobin concentration for this group of subjects was −0.07172, which is not a significant correlation. The range of hemoglobin concentrations for the group was 8.9 to 19.7 gm/100 cc. blood, with a mean of 14.6 ± 0.19; the range of fitness indices was 20.7 to 125.0, with a mean of 80.8 ± 1.59.

Hemoglobin Concentration and Response to Severe Exercise. The same 200 subjects also performed the Endurance Step Test (5). The endurance index time was noted for each subject and the endurance index pulse was calculated in each case. Again there was no evidence of a significant correlation between the hemoglobin concentration and the endurance index pulse or the endurance index time. The coefficients of correlation were −0.113 and +0.1686 respectively. The range of the endurance index pulse for the group was 13.3 to 38.2, with a mean of 25.4 ± 0.61; the range of the endurance index time was 35 to 132 seconds with a mean of 83.2 ± 2.15.

Hemoglobin Concentration and Response to Prolonged Moderate Exercise Exhaustion. Subjects can be fatigued by at least two types of muscular exercise. In the first place they may be asked to perform a rapid and severe form of muscular effort so that they acquire a rapidly increasing oxygen debt; or they can perform moderate exercise for a prolonged period. The former type of exercise is the basis of the Endurance Step Test; the latter type can be simulated by performing for prolonged periods the standard Harvard Step Test to exhaustion (6). Forty-six schoolboys (aged 14–20 years) were asked to perform this prolonged Harvard Step Test and the time of performance to exhaustion was noted in each case. To ensure adequate motivation, the exercise was made a competitive effort between rival schools. The coefficient of correlation between these times and the hemoglobin concentration for this group has a value of +0.4408, which is a significant correlation ($P = <0.01$). Therefore, we can say that for this group of subjects, the greater the hemoglobin concentration of the blood, the longer is the time of performance of moderate exercise which is required to produce exhaustion. The mean time of performance for the group was 457 seconds ± 39.0.

Hemoglobin Concentration and Strength. Strength has been assessed simply by the ability to lift a graded series of weights through a given height (20 inches) from the floor (5). The strength of the subject is then expressed simply

in terms of the maximum weight lifted. The coefficient of correlation between these strengths and the hemoglobin concentrations for 200 males and females was +0.3016, which is a significant value ($P = 0.01$). For the 120 males only, the coefficient of correlation was +0.440 ($P < 0.001$) and for the 80 females only, the coefficient was +0.061 ($P > 0.1$). Therefore, for males, but apparently not for females, the higher the blood hemoglobin concentration the greater the strength of the individual. The range of strength for the group was 50 to 205 pounds, with a mean of 117.4 pounds ±3.71.

DISCUSSION

We see, therefore, that the blood hemoglobin concentration is correlated significantly with speed of movement, strength and the ability to sustain prolonged, moderate muscular effort. This does not mean that the blood hemoglobin level is a necessarily important factor in determining speed, strength and endurance; a common causal factor, e.g. a good nutritional status, may be involved. It is possible to see how the response to prolonged muscular effort may be limited in part at least by the oxygen-carrying capacity of the blood, but it is difficult to see how the latter can be directly implicated in the determination of speed and strength.

It is interesting to recall our previous conclusions about these three aspects of physical fitness. Speed, strength and the ability to sustain prolonged muscular effort all increase with increasing age from childhood to reach a maximum in early adult life (6). The hemoglobin concentration shows a similar variation with age in these Ceylonese subjects (7).

In addition, subjects with a normal or stocky type of physique are in general faster, have a greater strength, and can maintain moderate muscular effort longer than can the other physical types. Again, the greater the muscular development of subjects, the greater their speed of movement and the greater their strength, while speed and the time for which moderate exercise can be performed to exhaustion are correlated in a highly significant manner (8). Moreover, males are faster than females and they have a greater strength at all ages; they also have consistently higher blood hemoglobin levels. There is, therefore, much evidence that the three aspects of physical fitness—speed, strength and the response to prolonged and moderate effort—together with the blood hemoglobin concentration are intimately related and are possibly based upon some common causal factor.

The hemoglobin concentration is not related significantly to the response of subjects to 5 minutes of moderate exercise (Harvard Test), nor to their response to rapid, severe exercise (Endurance Step Test). The former observation agrees with the conclusions of Spealman *et al.* (2) and is to be expected since the large reserve of oxygen-carrying power normally present in the blood of all but the most anemic of subjects will not be unduly strained by a short

burst of moderate exercise. We might have expected the response to rapid, severe exercise to be related to the hemoglobin level in the blood because, in this instance, a rapidly increasing oxygen debt is acquired. Presumably this type of exercise was so severe that the oxygen debt was too large to be influenced significantly by the rather small range of hemoglobin levels present in our group of subjects.

It should be noticed that these two aspects of physical fitness, which do not correlate significantly with the blood hemoglobin level, decrease with age, that both are correlated in a negative fashion with the muscular development of subjects, and that, whereas the response to moderate exercise is independent of physique type, the response to severe exercise is best in those subjects with a slim body build. This behavior contrasts with that of the three aspects of fitness which are correlated with hemoglobin level.

SUMMARY

The coefficient of correlation between the blood hemoglobin concentration and the responses to various exercise tests have been calculated for Ceylonese subjects aged 10 to 20 years. It is concluded that the blood hemoglobin concentration is correlated significantly with speed of movement, strength and the ability to sustain prolonged moderate muscular effort. There is no evidence for a significant correlation between the hemoglobin level and either the response to moderate exercise or the response to severe exercise.

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Relationship between Resting Pulse Rate, Blood Pressure and Physical Fitness

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PHYSICAL FITNESS is a vague term which is usually employed to denote the capacity of a subject for physical exercise. As there are many different types of physical exercise, there must be many varieties of physical fitness too. Some of the more obvious aspects of physical fitness include muscular strength, the ability to move with speed, the ability to perform moderate exercise, the ability to sustain rapid and severe muscular effort and the ability to maintain moderate physical effort to exhaustion.

It is usually assumed that a fit person has a slower resting pulse rate than his less fit colleague. Such an assumption is based upon comparisons which have usually been made between trained athletes and subjects engaged in sedentary occupations. In the experiments to be described, an attempt has been made to compare the resting cardiovascular state with the many different aspects of physical fitness, using normally active and healthy subjects aged 10 to 25 years inclusive.

METHODS

A thousand Ceylonese subjects performed the exercise tests. Since performance ability varies markedly with age and sex (1), the following groups were arranged among the 1000 subjects: age 10 years, 200 males and 50 females; age 14 years, 200 males and 50 females; age 17 years, 200 males and 50 females; age 21 to 25 years, 200 males and 50 females.

The tests performed included:

a) The Harvard Step Test (2) for 5 minutes, which is a moderate exercise test, and from the post-exercise pulse rates and systolic blood pressures, the fitness index pulse and the fitness index B.P. were calculated for each subject (3).

b) The Endurance Step Test, which is a severe exercise test (4), and for each subject's performance the following indices were obtained: endurance index pulse, endurance index B.P. and endurance index time.

c) The Harvard Step Test performed to exhaustion. The time of performance of each subject was recorded = exhaustion index time (1).

d) Strength was measured by lifting a graded series of weights a height of 20 inches from the floor; strength was then expressed in pounds weight lifted (1).

e) Speed was assessed by timing the subjects while running 100 yards (1).

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Before performing this battery of tests the sitting pulse rate and the sitting brachial blood pressure of each subject were recorded. The mode of the temperature was 80.2° F. and the mode of the relative humidity 76.0%.

RESULTS

Sitting Pulse Rate—Physical Fitness. In table 1 are given the calculated coefficients of correlation between the sitting pulse rate and the various estimates of the different aspects of physical fitness.

It is evident that the sitting pulse rate is not correlated significantly with speed of movement, nor with the response to severe exercise, nor with strength. It is correlated significantly with the fitness index pulse and possibly also with the fitness index blood pressure and the time for which moderate effort can

TABLE 1. CORRELATION BETWEEN SITTING PULSE RATES AND PHYSICAL FITNESS (1000 SUBJECTS)

PHYSICAL FITNESS INDEX	COEFFICIENT OF CORRELATION	LEVEL OF SIGNIFICANCE
		%
Fitness index pulse	−0.3740	0.1
Fitness index B.P.	+0.1977	5
Endurance index pulse	−0.1807	Not significant
Endurance index B.P.	+0.0733	Not significant
Endurance index time	−0.04212	Not significant
Exhaustion index time	−0.2002	5
Time to run 100 yards	+0.07062	Not significant
Strength	−0.06911	Not significant

be sustained. The correlation with the fitness index pulse means that those subjects with relatively slow resting pulse rates also have relatively slow post-exercise pulse rates, and vice versa.

Sitting Systolic Blood Pressure and Physical Fitness. The sitting systolic blood pressure is correlated significantly with the fitness index pulse, the fitness index blood pressure, speed of movement, the time for which moderate effort can be maintained and with strength (see table 2). It does not correlate significantly with the response to severe exercise. The correlation between the systolic blood pressure and the fitness index blood pressure is highly significant and expresses the fact that subjects with a relatively low sitting systolic blood pressure have a relatively low post-exercise systolic blood pressure, and vice versa.

The correlation between resting systolic blood pressure and the fitness index pulse is based upon the fact that resting pulse rate and resting systolic blood pressure are also related. Thus, for our group of subjects, the coefficient of correlation between resting pulse rate and resting systolic blood pressure is +0.4141. Calculation of the partial coefficient of correlation between the rest-

ing systolic blood pressure and the fitness index pulse, keeping the pulse rate constant, gives a value of 0.09727, which is not significant.

The greater the systolic blood pressure, the less is the time required to run 100 yards, that is, the greater is the speed of movement. Similarly, the greater the systolic blood pressure the longer the time for which moderate effort can be sustained and the greater the strength of the subject. We have already noted that speed, strength and the time for which moderate exercise

TABLE 2. CORRELATION BETWEEN SITTING SYSTOLIC BLOOD PRESSURE AND PHYSICAL FITNESS (1000 SUBJECTS)

PHYSICAL FITNESS INDEX	COEFFICIENT OF CORRELATION	LEVEL OF SIGNIFICANCE
		%
Fitness index pulse	−0.02378	2
Fitness index B.P.	−0.7180	0.1
Endurance index pulse	−0.006327	Not significant
Endurance index B.P.	−0.08694	Not significant
Endurance index time	+0.1660	Not significant
Exhaustion index time	+0.2063	<5
Time to run 100 yards	−0.3215	<1
Strength	+0.5710	<0.1

TABLE 3. CORRELATION BETWEEN SITTING DIASTOLIC BLOOD PRESSURE AND PHYSICAL FITNESS (1000 SUBJECTS)

PHYSICAL FITNESS INDEX	COEFFICIENT OF CORRELATION	LEVEL OF SIGNIFICANCE
		%
Fitness index pulse	−0.2946	<1
Fitness index B.P.	−0.5290	<0.1
Endurance index pulse	−0.03385	Not significant
Endurance index B.P.	−0.1047	Not significant
Endurance index time	−0.0231	Not significant
Exhaustion index time	+0.06164	Not significant
Time to run 100 yards	−0.1996	Not significant
Strength	+0.1742	Not significant

can be performed to exhaustion are all related in a similar manner to hemoglobin concentration, muscular development, physique and age (5).

Sitting Diastolic Blood Pressure and Physical Fitness. The sitting diastolic blood pressure is correlated significantly with the fitness indices but not with the endurance indices, speed, strength and the time of performance of moderate exercise to fatigue (table 3). Apparently for our group of subjects, the lower the resting diastolic pressure the greater is the fitness for moderate exercise, and vice versa. In this group the resting diastolic blood pressure is correlated significantly with the resting systolic blood pressure (coefficient of correlation,

$r = +0.5813$) but not with resting pulse rate ($r = -0.1321$). Calculation of the coefficient of partial correlation between the resting diastolic blood pressure and the fitess index pulse, keeping the pulse rate constant, and between the resting diastolic blood pressure and the fitness index B.P., keeping the systolic blood pressure constant, gives values of -0.3742 and -0.1970 respectively. The former is significant and the latter may be just significant ($P = 0.05$).

Sitting Pulse Pressure and Physical Fitness. The resting pulse pressure is not correlated significantly with the ability to move with speed, nor with fitness for moderate and severe exercise (table 4). There is some evidence of a correlation between the pulse pressure and strength. Pulse pressure and systolic blood pressure are correlated significantly ($r = 0.4007$ for this group of

TABLE 4. CORRELATION BETWEEN SITTING PULSE PRESSURE AND PHYSICAL FITNESS (1000 SUBJECTS)

PHYSICAL FITNESS INDEX	COEFFICIENT OF CORRELATION	LEVEL OF SIGNIFICANCE
		%
Fitness index pulse	−0.1319	Not significant
Fitness index B.P.	−0.1811	Not significant
Endurance index pulse	+0.1254	Not significant
Endurance index B.P.	+0.0471	Not significant
Endurance index time	+0.1426	Not significant
Exhaustion index time	+0.16923	Not significant
Time to run 100 yards	−0.09970	Not significant
Strength	+0.2511	2%

subjects) and calculation of the partial coefficient of correlation between strength and pulse pressure, keeping systolic blood pressure constant, gives a value of $+0.02952$, which is not significant.

DISCUSSION

We can conclude from the above results that the slower the resting pulse rate, the slower is the post-exercise pulse rate after a short period of moderate exercise. This agrees with the findings of most observers (6). Similarly, the lower the resting systolic blood pressure, the lower is the post-exercise blood pressure after 5 minutes of moderate muscular effort. On the other hand, the greater the resting systolic blood pressure the greater is the speed of movement, the strength and the time of performance of moderate exercise to fatigue. This observation stresses once more our postulate that the three aspects of functional fitness—speed, strength and the ability to perform prolonged muscular effort—have a common basis. They are usually performed better by sthenic types of subjects (1) and sthenic types have, usually, a greater systolic blood pressure, better muscular development and a higher hemoglobin level than do asthenic individuals (7). Homan (8) and Larson (9) similarly have reported

that sitting systolic blood pressure correlates significantly with fast swimming performance, while McKenzie (10) states that stronger individuals have a higher systolic blood pressure. However, it must be noted that most athletes cannot be distinguished from non-athletes by resting blood pressure alone (6), although it has been reported that hard training seems to produce a higher systolic blood pressure (11). Most studies of this factor have usually compared the trained athlete with a sedentary person. It is possible that such comparisons may be vitiated by the tendency of the blood pressure of sedentary adults to be raised from pathological or environmental causes.

Several studies have indicated that a relatively high resting diastolic blood pressure is a good index of fitness (6). The only significant relationship revealed by our experiments was the suggestion that the lower the resting diastolic pressure the greater is the fitness for a short period of moderate effort. We can offer no reasonable explanation of this divergency in results.

The range of resting pulse rates for our subjects was 62 to 110 beats per minute and the range of the resting systolic blood pressures was 76 to 128 mm. Hg. Our results can only be considered to be valid within these ranges and for the environmental conditions existing at the time of the tests. We have not quoted our results *in extenso* for the two sexes and the various age groups. Very similar results were obtained for both sexes and at all the ages studied.

SUMMARY

One thousand Ceylonese subjects, aged 10 to 25 years and of both sexes, performed a series of exercise tests. It has been concluded that the slower the resting pulse rate or the lower the resting systolic blood pressure, the slower is the post-exercise pulse rate or the lower is the post-exercise systolic blood pressure, respectively. Speed of movement, strength and the ability to sustain moderate exercise are positively correlated with the resting systolic blood pressure.

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Lung Function Studies. III. Uneven Pulmonary Ventilation in Normal Subjects and in Patients with Pulmonary Disease[1]

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VARIOUS INVESTIGATORS, using fractional (1–4) or continuous (5) analysis of alveolar gas exhaled on a single expiration, have agreed that the lungs are not ventilated evenly in normal subjects, i.e. that inspired gas is not evenly distributed throughout the lung gas. The two principal explanations have been *1*) that the inspired gas is layered (stratified) in each unit of the lung so that there is a higher concentration of inspired gas in the alveolar ducts than in the alveolar sacs (1), and *2*) that the inspired gas is distributed unevenly to different lobes or lobules of the lungs (2); regional differences in ventilation have been thought to arise because the per cent change in volume varies in different areas of the lung during inspiration (4). Roelsen found that patients with bronchial asthma and pulmonary emphysema showed greater variation in the composition of successive portions of expired alveolar gas than did normal subjects; he attributed this to a greater inequality of intrapulmonary gas mixing (2).

Reinvestigation of this problem has been carried out to obtain quantitative data on this lack of uniformity of alveolar gas in normal subjects, to learn more concerning the mechanism by which this is produced, and to devise a test which might prove of value in the differentiation of normal intrapulmonary gas mixing from that occurring in patients with certain types of pulmonary disease.

The studies to be reported confirm the presence of uneven lung ventilation in normal subjects, apparently on a regional basis. However, they indicate that preferential distribution of the dead space gas to certain areas of the

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lungs may occur regularly and to some extent be responsible for the inequality. In addition, a 'uniformity index' is proposed for the measurement of intrapulmonary gas mixing; this index has been calculated for a group of normal subjects. Although not a direct quantitative measure, it has served to identify abnormal intrapulmonary gas mixing in patients. Since the test is objective, requires little cooperation on the part of the patient, and takes only a few minutes, it may be valuable as a rapid screening test for particular types of pulmonary disease.

METHODS

General. The method has been described previously (6). In brief it consists of continuous analysis and photographic recording of *1*) expiratory volume flow, and *2*) N_2 concentration of respired gases during and after the change from breathing room air to breathing 99.6 per cent O_2. The Lilly-Hervey nitro-

TABLE 1. NORMAL VARIATIONS IN EXPIRED ALVEOLAR N_2 CONCENTRATION AFTER MAXIMAL INSPIRATION OF O_2

POINTS COMPARED	MEAN ± S. D.	
	N_2 Difference	Uniformity Index
	%	
$alv_{750} - alv_{1250}$	0.75[1]	1
$alv_{750} - alv_{\frac{1}{2}TC}$	2.4 ± 0.5	0.852 ± 0.040
$alv_{750} - alv_b$	5.0 ± 1.4	0.725 ± 0.066

[1] S. D. and uniformity indices were not calculated, since the variations (0.5 to 1.5% N_2) approached the error of measurement.

gen meter (7), used in these studies, is not sensitive enough to detect accurately the slight changes in N_2 concentration that occur in respired air during the respiratory cycle, when room air is breathed. However, when the inspired gas, to be mixed with alveolar gas (80% N_2), is not air, but O_2 (0.4% N_2), the effect of uneven mixing is magnified so as to be readily detected with this instrument.

Studies were performed with the subjects in the sitting position, except when noted otherwise. At the beginning of each test, the subject breathed room air for several minutes through a mouthpiece attached to a 4-way valve. During an expiration, the room air orifice was closed, so that O_2 was breathed on the following inspiration and thereafter. In special experiments (table 2), in addition to the routine measurements of expiratory volume flow, inspired volumes were measured from a 6-l. recording spirometer used as the source of O_2. For experiments in which positive expiratory pressure was developed by expiring against a water column, the flow meter calibration was calculated from direct spirometric measurement of total expired volume.

Instrumental. The characteristics of the flow meter and N_2 meter have been described previously (6). Measured points were separated in time by at least 0.5 second, which is at least 5 times the instrumental lag. The N_2 concentrations were measured to the nearest 0.5 per cent, corresponding to about 0.5 mm. change on the record. On the basis of Roelsen's data (8), we have assumed that, when the subject is breathing room air, the concentration of N_2 in alveolar gas after a 650-ml. expiration is 80 per cent and have calibrated each record on this basis.

Measurement of Records. The uniformity index, to be described, compares the composition of alveolar gas at two different points during the first expiration following inhalation of O_2. The method of selecting these points is consequently a matter of importance for it is essential that both represent alveolar gas uncontaminated with dead space gas. Figure 1, obtained upon a healthy adult, shows a typical record and the method of measurement. During the first part of the record, air is breathed, the N_2 concentration appears to be

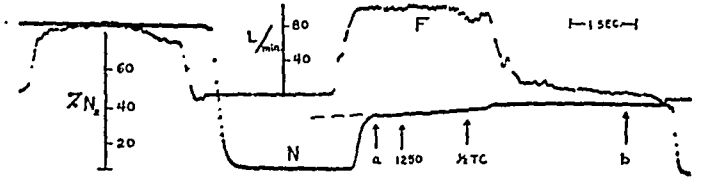

Fig. 1. Record of expiratory volume flow (F) and N_2 concentration (N) during voluntary hyperventilation. *Read left to right.* First, expiration after air breathing, then inspiration of O_2, then maximal expiration. For labels under arrows, see text.

uniform throughout the expiration and is assumed to be 80 per cent. Then O_2 is inspired. On the next expiration, 20 to 100 ml. of undiluted O_2 are expired, followed by several hundred milliliters of gas with a rapidly rising N_2 content, and finally by gas with a relatively uniform N_2 content. The first two phases represent washing out of the respiratory dead space, and the last phase, or plateau, is considered to represent 'alveolar' gas. These three phases are not readily identifiable in all individuals, especially those with pulmonary emphysema. However, when they are clearly separable (most normal subjects), the point on the curve representing the first pure alveolar gas can be located quickly by the following method.

The point at which the S-shaped curve meets the alveolar plateau is selected by drawing a straight line on the photographic record along the top of the plateau; the N_2 concentration at the point where the plateau line becomes tangent to the rising S-shaped curve is assumed to represent the first pure alveolar gas (alv_a). When expired volume is large, the straight line is sometimes drawn along only the first half of the plateau, since the N_2 curve in the later part of expiration may change its slope in relation to volume, or

the terminal reduction in volume flow may change the slope of N_2 increase in relation to time. The justification for this procedure follows.

Since we are concerned with alveolar ventilation, a ventilatory criterion is needed to define pure alveolar gas. In terms of ventilation, alveolar gas is 'pure' if it has no admixture of gas from the anatomical dead space. The presence of such admixture can be determined as follows.

During inhalation of O_2, the N_2 concentration of alveolar gas is progressively reduced on successive breaths. This change in alveolar N_2 concentration can be assumed to be expressed by the equation $C_n = C_0 r^n$,

where C_0 = initial alveolar concentration, about 80 per cent N_2;
C_n = alveolar concentration after n inhalations of O_2;
r = alveolar dilution ratio (9).

For the first several breaths of O_2, slight variations resulting from the presence of N_2 (0.4%) in the inspired gas and the elimination of blood N_2 can be neglected. Thus log C_n plotted against n should give a straight line, passing through 80 per cent N_2 at n_0, if the concentrations selected represent pure alveolar gas. When concentration points were selected from similar portions of the first part (O_2) of successive expired N_2 curves, C_0 was obviously zero (0.4%). When the N_2 concentrations were selected at about the midpoint of the S-shaped curve, C_0 was 40 per cent N_2. For N_2 concentrations selected at the point at which the S-shaped curve meets the alveolar plateau, C_0 was 80 per cent N_2, and so meet this definition of alveolar gas. The equation is based on certain assumptions, including constancy of tidal, dead space and functional residual volumes. These results also apply only to the first several breaths of those normal individuals whose measured tidal volume was fairly constant, and are subject to the limits of accuracy of N_2 measurement. In some cases C_0 varied somewhat from 80 per cent (78.5–81%), but was the same for various points on the alveolar plateau; this indicates that early points on the plateau are as nearly pure alveolar gas as the end-tidal points.

In patients with pulmonary disease and marked unevenness of gas mixing, alv_a usually cannot be selected as above, as can be seen in figure 3. It is necessary that the expired volume preceding alv_a be sufficient to wash out completely the anatomical dead space, so that alv_a is uncontaminated with dead space gas. The wash-out volume has been found in normal subjects to have an average value of 325 ml. (S.D. ± 65 ml.) during quiet breathing (6), or 526 ml. (S.D. ± 118 ml.) during maximal inspiration and expiration (see the section on RESULTS). With maximal lung inflation the dead space and the volume required to wash it out on expiration are enlarged. Thus, on a patient's record an expired volume of 750 ml. is marked on the flow record and the simultaneous point on the N_2 record is considered to be alv_a; 750 ml. is chosen because it represents approximately the mean normal wash-out volume plus

2 S.D. This method does not identify the first portion of pure alveolar gas, but statistically insures that 95 per cent of such points represent alveolar gas uncontaminated with anatomical dead space gas; when alv_a is obtained in this way, it is identified as alv_{750}. The assumption that the volume required

TABLE 2. EFFECT OF RESPIRATORY VARIABLES ON UNIFORMITY OF EXPIRED ALVEOLAR GAS[1]

TYPE OF EXPERIMENT	SUBJ.	NO. OF EXPTS.	INSP. VOL.	INSP. TIME	MAX. EXP. FLOW	A: Total exp. alv. vol. (maximal exp.) Differences between alv_a and alv_b				B: Terminal exp. alveolar vol. Differences between alv_a and alv_b — vol. in col. 2			
						N_2	Vol.	Time	Unif. Index	N_2	Vol.	Time	Unif. Index
			ml.	*sec.*	*l/min.*	%	*ml.*	*sec.*		%	*ml.*	*sec.*	
Increasing inspired vol. normal pre-inspiratory lung volume	1	2	240	1.6	34	3.5	840	3.0	0.47	3.5	840	3.0	0.47
		3	520	1.5	44	4.0	950	2.7	0.67	4.0	950	2.7	0.67
		2	1720	3.9	57	7.25	2240	3.8	0.69	5.0	950	2.6	0.78
		2	2700	6.5	62	7.0	3100	5.0	0.70	3.5	950	3.0	0.80
	2	2	770	2.1	38	3.5	1940	4.8	0.80	3.5	1940	4.8	0.80
		2	1950	2.6	37	4.75	3020	8.0	0.79	2.75	1940	4.3	0.89
		1	2450	4.0	42	3.5	3250	8.5	0.84	1.5	1940	4.4	0.93
Varying inspiratory time by breathholding	1	3	825	3.0	70	6.5	1875	3.5	0.63				
		2	830	13.0	76	4.75	1825	4.5	0.70				
		2	830	22.0	76	3.0	1810	3.6	0.81				
		1	855	32.0	72	2.0	1850	6.0	0.86				
	2	2	830	2.5	80	3.75	1610	3.0	0.78				
		2	950	13.0	77	2.5	1710	2.8	0.87				
		2	900	22.0	65	2.25	1350	3.3	0.88				
Varying expiratory rate	1	2	980	3.3	31	6.25	1450	4.0	0.66				
		2	930	3.5	74	3.75	1440	2.5	0.77				
	3	2	750	5.0	20	4.25	1610	9.1	0.70				
		2	750	7.5	80	1.75	1590	2.2	0.86				
Added dead space; small pre-inspiratory lung volume													
none added	1	2	895	2.5	40	3.75	790	3.9	0.83				
150 ml. added		2	875	2.0	53	5.0	745	3.4	0.77				
350 ml. added		2	875	1.9	38	9.75	760	3.7	0.53				
none added	4	2	1350	4.5	61	3.5	1430	4.0	0.84				
350 ml. added		2	1290	3.8	55	4.25	1320	4.6	0.77				

[1] All figures are average values.

to wash out the dead space is not greater in patients than in normal subjects is supported by experimental data.

Other N_2 concentrations, used for comparison with alv_a or alv_{750}, may vary according to the circumstances of the study. One such point can be the highest N_2 concentration on the plateau, found at or very near the end of expiration; this is called alv_b. The volume of expired gas between alv_a and alv_b can be variable; therefore in a few special studies (table 2), the points

compared were alv_b and a point at a measured volume preceding alv_b. These points are designated as alv_b minus the volume indicated (e.g. $alv_b - 1000$).

Many patients with cardiopulmonary disease have a reduced vital capacity an increased residual capacity, and cannot expel as large a fraction of their total lung capacity as normal subjects. It seemed advisable to have additional measurements on normal subjects which could be used for comparing similar fractions of the total lung gas. Two such measurements were made for the normal subjects who made maximal inspirations and expirations. The first was the N_2 concentration at 1250-ml. expired volume (alv_{1250}); most adult patients can expire 1250 ml. or more in the vital capacity procedure. N_2 concentrations were also measured at a total expired volume equal to 50 per cent of the total lung capacity, estimated from age and vital capacity (10); this point is called $alv_{\frac{1}{2}TC}$, and was at an average expired volume of 2760 ml.

Calculation of Results. In any system the dilution of contained N_2 by added O_2 can be represented by the equation

$$C_F = C_i \frac{V_i}{V_i + V_a}$$

where
C_i = initial N_2 concentration
C_F = final N_2 concentration
V_i = initial volume
V_a = added volume of O_2.

Rearranging, $\frac{V_a}{V_i} = \frac{C_i - C_F}{C_F}$. This may be called the 'dilution index'. For example, if one liter (V_a) of O_2 is added to one liter (V_i) of gas containing 80 per cent N_2 (C_i), C_F becomes 40 per cent and $\frac{80-40}{40} = 1.0$. If only 600 cc. of O_2 is added to one liter of 80 per cent N_2 gas, C_F becomes 50 per cent so $\frac{80-50}{50} = 0.6$. In both cases the magnitude of dilution is expressed quantitatively by the dilution index. Comparison of dilution in two systems can be expressed as the ratio of the respective dilution indices, which may be called the uniformity index. Here this is $\frac{0.6}{1.0}$, or the added O_2 per unit of initial volume in the second case has been only 0.6 of that in the first case. In RESULTS, uniformity index $= \frac{\text{dilution index of late expired gas}}{\text{dilution index of early expired gas}}$. In all cases, 80 per cent has been used as the initial concentration. A uniformity index can be computed for any two alveolar concentrations among those measured (alv_a, alv_{750}, etc.). However, for normal subjects, uniformity indices have not been calculated for $alv_a - alv_b$ with quiet breathing, or $alv_{750} - alv_{1250}$ with hyper-

ventilation, since the differences in N_2 concentration were small and approach the error of measurement.

RESULTS

Uniformity of Expired Alveolar Gas in Normal Subjects. Records were obtained from 45 healthy while males, aged 19 to 38 years, who were breathing naturally. On the first expiration after O_2 inhalation, the expired volume of 5 subjects was insufficient to wash out the dead space and the alveolar plateau therefore was not evident; measurements were made at alv_a and alv_b on the records of 40 subjects. The N_2 plateau was approximately linear in 36 subjects, was wavy in 3 cases, and in one case showed a sudden step-like rise late in expiration without coincident change in volume flow. In all, the N_2 concentration at alv_b was equal to or greater than that at alv_a; the average increase was 1.64 per cent with a standard deviation of $\pm$0.84 per cent. Both the slope of the plateau and volume of expired gas between the measured points were variable.

Thirty measurements were also made on 18 healthy subjects (6 female, 12 male, age 17 to 73, average 33.7 years) during maximal expiration following maximal inspiration of O_2; velocity of breathing was not controlled. These subjects were semi-reclining, with the head and trunk elevated 50–60 degrees above the bed. This position was selected because it is satisfactory for dyspneic as well as for normal subjects. Average values were: total expired volume, 4330 ml.; volume to alv_{ITC}, 2760 ml.; volume to alv_a, 526 ml.; S.D. $\pm$118 ml. (all BTPS). In every case the N_2 concentration of the alveolar plateau increased almost linearly with respect to volume throughout most of the expiration, although during the last several hundred milliliters it increased more steeply in some and decreased slightly in others. The results of N_2 measurement are given in table 1. The uniformity indices were reproducible; the S.D. of differences between duplicate measurements ($alv_{750} - alv_b$) and their mean was 0.022 in 12 subjects.

Factors Influencing Uniformity of Expired Alveolar Gas. The increasing alveolar N_2 concentration later in expiration indicates that inspired O_2 is not evenly distributed throughout the functional residual gas and also that the relatively poorly ventilated areas of the lung empty proportionately more in late expiration. The following experiments were performed to determine the effect of varying volume, time and velocity of inspiration and expiration upon the uniformity of expired alveolar gas.

The best controlled experiments are listed in table 2; column A gives the differences in % N_2, volume and time between alv_a and alv_b; expirations were always maximal. Comparison of uniformity indices in column A is valid except for the experiments with increasing inspired volume, in which the uniformity indices in column B should be used, since the latter have been computed for

equal volumes of gas expired at the same level of lung inflation. In 21 pairs of duplicate experiments on *subject 1*, the S.D. of the differences between duplicate uniformity indices and their means was 0.023, and in the 14 pairs of duplicate experiments on *subject 2* was 0.024. Thus a difference between the means of duplicate indices, as listed in table 2, must equal or exceed 0.05 to be significant.

a) Inspiratory variables. It will be noted that as inspired volume increased, the uniformity of expired alveolar gas increased, i.e. the uniformity index approached unity (column B), although there was a diminishing effect with increasing volumes.

As inspiratory time was prolonged by breathholding for 10 to 30 seconds, the variation in N_2 concentration decreased, but was still 2 to 3 per cent N_2 after 20 to 30 seconds of breathholding. Similar experiments were done by 5 other subjects, comparison being made between uniformity indices of maximal expirations following *a)* immediately and *b)* 20 seconds after inspiration. In all, the uniformity index was greater after breathholding but did not reach unity. The mean increase was 0.154, with a significant *t* value of 4.3. Although inspired volume was not measured in these 5 subjects, the similarity of N_2 concentrations and total expired volumes indicated that it had not varied by more than 100 to 200 cc. between the comparative experiments; peak expiratory flow was voluntarily controlled and found similar on measurement. Other inspiratory variables were tested without observing any significant effect. These included rate of inspiratory volume flow (8 experiments, 2 subjects); preinspiratory lung volume (12 experiments, 2 subjects); inspiratory flow and time (8 experiments, 2 subjects); and positive (8 cm. H_2O) inspiratory pressure (5 tests, 7 control experiments, 1 subject).

b) Expiratory variables. When a maximal expiration was made evenly, alveolar N_2 concentration increased almost linearly with respect to both time and expired volume during the major part of the expiration (fig. 1). However, rapid expiration produced a more horizontal plateau than slow expiration (table 2). Experiments varying the rapidity of expiration were also done by 7 other subjects. With slow expiration the average peak expiratory flow was 34 l/minute, and with rapid expiration was 115 l/minute. In all cases the uniformity index ($alv_a - alv_b$) was greater with a rapid expiration; the mean increase was 0.17, with a highly significant *t* value of 4.6.

When a normal quiet expiration was followed immediately by a further forced expiration, as in giving an 'end-expiratory' alveolar sample, the N_2 concentration no longer increased evenly in respect to volume, but increased rapidly early in the forced expiration, and then remained almost constant during the rest of the expiration. Such results were found in 6 of 9 normal subjects; in 3 the slope remained constant despite the interposed forceful expiration. In one subject, a small increase in uniformity was found with positive expira-

tory pressure (10 cm. H_2O); the mean uniformity index 0.68 of 7 experiments was significantly greater than the mean index 0.65 of 7 control experiments.

Cause of Nonuniformity of Expired Alveolar Gas. In addition to the explanations previously offered ('stratification' and 'regional' concepts) there is another way in which nonuniformity could arise, even though the per cent increase in volume during inspiration is equal in all sections of the lung. From experiments on one normal subject, Rauwerda concluded that certain areas of the lung fill mainly during the first part of inspiration, and other areas fill mainly during the latter part of inspiration. This process we shall call 'sequential ventilation'. He also observed that the areas which fill during early inspiration are less well ventilated than the areas which fill later. On this basis the following possibility is suggested.

It is certainly reasonable to believe that the dead space gas enters the alveolar spaces first, and the fresh inspired gas (O_2 in our studies) follows. If certain areas of the lung fill first, they may receive more of the dead space gas, while the areas which fill later receive more of the O_2. Then regional differences in alveolar gas composition will arise toward the end of inspiration even though the final percentage increase in volume is equal in all areas. This sequential filling process can be detected by examination of the expired alveolar gas only if there is also sequential emptying. The results above show that sequential emptying does occur, with relatively poorly ventilated areas emptying preponderantly later in expiration. If the higher N_2 concentration in these areas had resulted from preferential distribution of the dead space (80% N_2) gas to them, it would be required that the areas which fill first on inspiration also empty last on expiration.

This concept of sequential ventilation was tested by studies in which the sequence of inspired gases was reversed. Inhalations were made consisting of several hundred milliliters of O_2, followed without interruption by several hundred milliliters of room air. When such inhalations began at the normal expiratory position, the usual rising N_2 concentration late in expiration was found; however, when inspiration began at an extreme expiratory position, the slope of the alveolar plateau was reversed. Instead of the usual rising N_2, now a decreasing N_2 concentration later in expiration was found; reversal of the alveolar N_2 slope was obtained in duplicate experiments on 3 normal subjects. This confirms Rauwerda's results and the 'first-in, last-out' possibility. When the gas that entered first contained 80 per cent N_2 (dead space) and the gas that entered last was O_2, a higher N_2 concentration was found in the last expired gas. When the gas that entered first was mainly O_2, and the gas that entered last contained 80 per cent N_2, a lower N_2 concentration was found in the last expired gas. This procedure was also used on 5 persons having pulmonary disease (asthma, chronic bronchitis, emphysema). Maximal inspira-

tions and expirations were made (average 1790 ml.); inspired gas was either all O_2, or the first half was O_2 followed without interruption by room air. After inhalation of O_2 alone, the plateaus showed considerable upward slope. However, after the O_2-air inhalations, the plateaus in every case were more nearly horizontal. Uniformity indices, calculated from N_2 concentrations at 750 ml. and end-expiration, were, with O_2-air inhalations, increased an average of 0.196, with a highly significant t value of 7.8. These changes are of course similar in direction to those in normal subjects.

If variations in the composition of alveolar gas were due solely to sequential filling, the volume of the dead space should limit the extent of variation, and greater variation would be expected when the dead space was increased. Experiments on 2 normal subjects were made in which dead space was added by interposing air-filled rubber tubing between the 4-way valve and the source of O_2. When inspiration began at the normal expiratory level, the addition of 150 or 350 ml. of dead space did not affect the uniformity of expired alveolar gas; however, when inspiration began at a deep expiratory position, more variation in composition was found with added dead space (table 2). Eight subjects with chronic pulmonary disease made vital capacity inspirations and expirations (average 2580 ml.); inspired gas was, in each subject, either all O_2, or 650 ml. dead space was added. Comparison of uniformity indices, calculated from N_2 concentrations at 750 ml. and end-expiration, showed them to be smaller in all cases with added dead space. The mean decrease, 0.06, was highly significant, having a t value of 4.9.

DISCUSSION

In these studies, N_2 concentration of expired gas always increased, with continued expiration, when O_2 had been inhaled on the preceding inspiration. Before this finding can be interpreted validly in terms of alveolar ventilation, certain points require consideration. The phenomenon does not appear to be an artefact for the following reasons. *a*) The increase is much slower than the instrumental lag. *b*) After inhalation of room air, alveolar N_2 content is approximately constant during normal or forced expiration. *c*) After breathing O_2 for several minutes and then inhaling one breath of room air, the expired alveolar gas regularly shows a decreasing N_2 content later in expiration. *d*) After a large inspiration of O_2, the N_2 concentration of 3000 ml. of expired alveolar gas may rise by 7 per cent; this would represent an addition of at least 105 ml. of N_2 or 133 ml. of air, which is too large to have come from pulmonary venous blood, lung tissue or the oronasal cavities, or to be attributed to an R.Q. effect.

The increasing N_2 content cannot represent a decreasing amount of admixture with O_2 from the respiratory dead space, 'pure' alveolar gas being expelled only at the extreme end of expiration, as Armitage and Arnott suggest

(11), for reasons discussed under the section on METHODS. Furthermore, the addition of more than 400 ml. of O_2 would be required, during a 3000-ml. expiration, to depress the plateau concentrations an average of 3.5 per cent N_2 below that of the pure alveolar gas, represented by alv_b. This volume, 400 ml., added to the 150 to 200 ml. of O_2 expired prior to the plateau, is much greater than the volume of the respiratory dead space.

Thus, one may conclude that the plateau represents alveolar gas and that the variations in expired alveolar N_2 concentrations, by exclusion, must be

TABLE 3. ILLUSTRATION OF VENTILATION MECHANISMS[1]

BEFORE INSPIRATION			INSPIRATION							AFTER INSPIRATION		MECHANISM
	Vol.	N_2	No.	Lung Area	Vol. added DS	Vol. added O_2	DS/O_2	Expansion	Vol. Change	Vol.	N_2	
	ml	%						*ml*	%		%	
Dead space	120	80	1	upper	40	320	1/8	360	100	720	varies	Uneven ventilation due to stratification
				lower	80	640	1/8	720	100	1440	varies	
Upper lung area	360	80	2	upper	40	320	1/8	360	100	720	44.4	Even ventilation with uneven expansion
				lower	80	640	1/8	720	100	1440	44.4	
Lower lung area	720	80	3	upper	20	340	1/17	360	100	720	42.2	Uneven ventilation due to different % vol. change
				lower	100	1700	1/17	1800	250	2520	26.0	
			4	upper	120	240	1/2	360	100	720	53.3	Uneven ventilation due to preferential distribution of dead space gas
				lower	0	720	0	720	100	1440	40.0	

[1] See figure 2 and text.

attributed principally to unequal distribution of O_2 throughout the functional residual gas.

These studies confirm previous findings that the lungs are unevenly ventilated in most healthy subjects, even during a maximal inspiration. The average uniformity index, 0.725, is similar to the magnitude of variation in composition of expired alveolar gas reported by Roelsen and Mundt. However, the observed variations in N_2 concentration during an expiration represent only the minimal variations which could have existed in the lungs at end-inspiration. For example, marked regional differences could exist in the composition of alveolar gas, but go unnoticed if the proportion of gas delivered to the expired gas from each region remained constant throughout expiration. Since the N_2 concentration does increase later in expiration, the proportion must be changing progressively in favor of poorly ventilated areas. However, the change

in proportion, or the relationship between the emptying of various areas can be altered. The sudden increase in N_2 concentration with an interposed forceful expiration indicates that emptying of poorly ventilated areas is promoted to a greater degree than that of well ventilated areas. When the total expiration is more rapid, the increased gas uniformity suggests that poorly ventilated areas are emptied early in expiration to a greater extent than when expiration is quiet. Mundt's failure to note the effect of changes in expiratory rate may have been due to the use of H_2, or to comparing only the differences in the last liter of a maximal expiration. The slope of N_2 increase in the last liter is not always equal to that in alveolar gas expired earlier and may not show changes which are evident in the total expired alveolar gas; with this Rauwerda agrees.

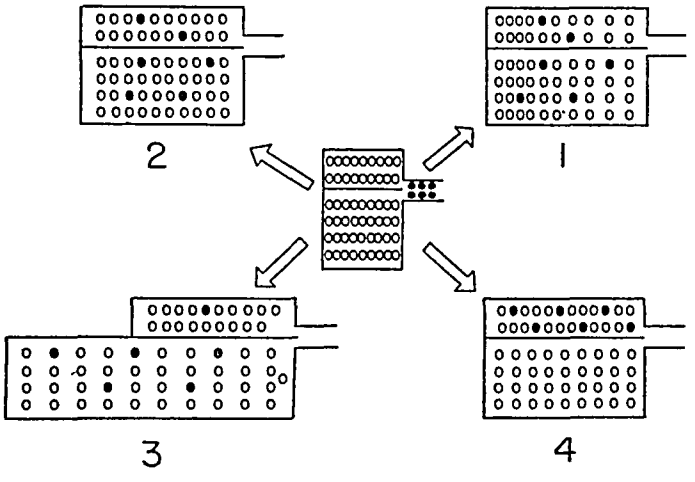

Fig. 2. VARIOUS MECHANISMS OF PULMONARY VENTILATION. Open and closed circles represent N_2 molecules. Central figure shows pre-inspiratory conditions in 2 lung areas and dead space. Figs. 1–4 correspond to conditions in table 3, after inspiration of a N_2-free gas (O_2). See text.

If analysis of the expired gas is used to determine whether end-inspiratory variations in alveolar gas composition can be changed, expiration must be controlled. Although the expiratory flow pattern is obviously an incomplete registration of the emptying process, similarity of flow patterns is at least some indication of a similar emptying process, and appears to be one of the requirements for reproducing the alveolar plateau. With such control, it appears that larger inspired volumes promote equality of alveolar ventilation. This is compatible with either of the theories of unequal ventilation.

There are two main theories concerning the mechanism of uneven ventilation. The first states that the inspired gas is layered or stratified in each individual air unit throughout the lung so that there is a higher percentage of inspired gas in each duct and atrium than in the slightly more peripheral alveolar sacs; this might give rise to a progressive increase in N_2 concentration throughout expiration (table 3, fig. 2, *mechanism 1*.) However, Rauwerda believes this theory to be untenable, since his calculations showed that, within one second, diffusion would obliterate any differences existing within the unit consisting of an alveolar duct and its alveolar sacs. He showed that during 15

to 30 seconds of breathholding after O_2 inhalation, the differences in alveolar gas concentrations are reduced, but not eliminated; our results using similar periods of breathholding confirm this with respect to N_2. He concludes that differences which disappear have done so by diffusion inside individual lobules or between adjacent lobules; the differences which do not disappear represent variations in the composition of gas in more widely separated areas of the lung.

The second, and more likely, concept is that regional differences exist, namely that inspired gas is distributed unevenly to different lobes or lobules of the lung. In 1909 Keith (12) pointed out that the expansion of various parts of the lung may be unequal, since the lung is composed of elements of varying degrees of distensibility. The root zone, containing large bronchi and vessels and much fibrous tissue, offers greater resistance to a distending force than the peripheral subpleural zone. It must be remembered, however, that unequal expansion will produce unequal ventilation in different regions only when the percentage increase in volume varies in the different areas of the lung. In that case, non-uniformity of alveolar gas would occur (2, 4). These mechanisms are illustrated in figure 2, *mechanisms 2 and 3.*

There is also another way in which regional differences in composition could arise, even though the percentage increase in volume was equal in all sections of the lung (fig. 2, *mechanism 4*). This results from sequential ventilation, which indicates that certain areas of the lung fill before, and empty after, other areas. When sequential filling occurs early in inspiration, the first gas entering the alveolar spaces (dead space gas) is distributed preferentially to those regions which expand first. Experimental evidence has been obtained which supports this mechanism as being a cause of uneven alveolar ventilation in both normal subjects and in patients with pulmonary disease. However, such evidence was obtained in normal subjects only when inspiration began at an extreme expiratory position, but not at the normal expiratory position. The cause of this difference is not apparent. The regional intrathoracic distribution of various forces interacting to cause gas flow in and out of the lungs is not well understood, either with respect to magnitude, time course, or variation at different levels of lung inflation.

If variations in alveolar gas composition were due solely to inequality in the percentage increase in volume, it is not apparent why the variations should be affected by changing either the sequence of inspired gases or the volume of the dead space. It is possible that both mechanisms, unequal percentage changes in volume and sequential ventilation, occur. The uniformity of the composition of alveolar gas would then depend on the relative magnitude and spatial distribution of the two processes.

When breathing air, the O_2 content of alveolar gas depends on both the loss to the pulmonary blood (perfusion) and the gain from the inspired air (ventilation). Although the results above measure only the ventilation factor,

they suggest some of the variables which may be involved in obtaining reproducible Haldane-Priestley alveolar samples, a procedure which is well known to require considerable training. The marked variation present in a single alveolar expiration emphasizes that a single small sample of alveolar gas may not be representative of the total expired alveolar gas. Rahn and associates (13) found concentrations of O_2 in alveolar gas to decrease in order when samples were obtained *1*) at the end of normal tidal volume, *2*) at the end of forced expiration begun at end-inspiration, and *3*) at the end of forced expiration begun at end-expiration. The differences were attributed to the time required for the forced expiration. The significance of the differences between various types of alveolar gas samples is currently debatable. Barker *et al.* (14) found the pCO_2 to be lower in the end-tidal samples than in arterial blood,

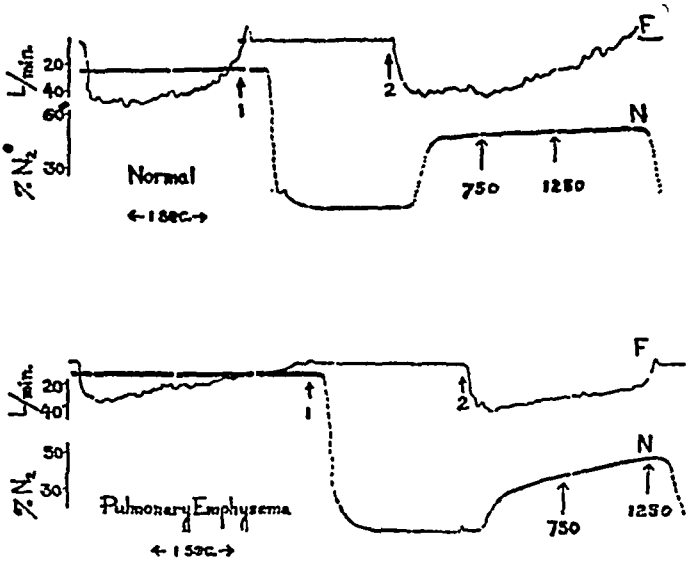

Fig. 3. RECORDS OF EXPIRATORY VOLUME FLOW (*F*) and N_2 concentration (*N*) during voluntary hyperventilation. First, expiration after air breathing, then (1–2) inspiration of O_2, then expiration. N_2 concentration at alv_{1250} exceeds alv_{750} in the normal record by 1 per cent, in the emphysema record by 9 per cent.

and Forssander and White (15) believe that end-tidal samples are diluted with air from the dead space. However, Rahn (16) found close agreement between end-tidal and arterial tensions. The present studies indicate that end-tidal gas comes chiefly from well-ventilated alveoli. As Roelsen pointed out (8), alveolar gas samples at the end of a deep expiration come from relatively poorly ventilated alveoli. In such a terminal sample of expired gas, gas from poorly ventilated alveoli will be represented to a greater extent *a*) when the total expiration is slower, and *b*) in end-expiratory Haldane-Priestley samples than in end-inspiratory samples. The latter is because the normal tidal expiration empties mainly well ventilated alveoli; this gas is not available for admixture in the end-expiratory sample.

The experimental procedure used in the study of normal subjects has been extended to an investigation of patients suspected of having abnormal alveolar ventilation. The patient is asked to make a maximal inspiration of O_2 and

follow this by a maximal expiration (vital capacity procedure). N_2 concentrations are measured at alv_{750}, alv_{1250}, and at alv_b. Our studies confirm Roelsen's finding that patients with bronchial asthma and pulmonary emphysema show much greater variation in the composition of alveolar gas than do normal subjects (fig. 3). In normal subjects, the difference between alv_{1250} and alv_{750} is not more than 2 per cent N_2; this may increase to 3 to 4 per cent in patients with uncomplicated bronchial asthma and to 10 per cent in patients with marked pulmonary emphysema. For reasons noted previously in the section on METHODS, these differences have not been expressed as uniformity indices. However in the range of N_2 concentrations usually found, 20 to 50 per cent, the relationship between percentage N_2 differences and uniformity indices is such that larger percentage N_2 differences correspond roughly to smaller uniformity indices. The normal uniformity index, calculated for alv_{750} and alv_b is 0.725 (S.D. $\pm$ 0.066), and may decrease to 0.50 in some patients with asthma and to 0.25 in patients with severe emphysema. If the total lung capacity has been measured, the uniformity index calculated for alv_{750} and $alv_{\frac{1}{4}TC}$ is useful, particularly in patients having slightly abnormal plateaus. Such patients may expel only 50 to 60 per cent of the total capacity and the uniformity index ($alv_{750} - alv_b$) may be 0.65 to 0.75. Such values are compared better with the normal index for $alv_{750} - alv_{\frac{1}{4}TC}$, which is 0.852 (S.D. $\pm$ 0.04) than with the normal index for $alv_{750} - alv_b$ (0.725 $\pm$ 0.066), which represents expulsion of about 80 per cent of total capacity. Detailed data upon patients will be presented elsewhere.

Findings in patients such as these were attributed by Roelsen to increased variation of alveolar ventilation. However, variations in the composition of expired alveolar gas depend not only on uneven ventilation but also on the relations between the emptying of different areas of the lung. Thus the differences might not be solely the result of greater variations in alveolar ventilation, but be entirely or partially due to different emptying patterns; qualitatively, this is unlikely, since other evidence (9, 17) indicates the presence of abnormal ventilation in emphysema. However, at present this limits the validity of using the variations in compositions of expired alveolar gas as a quantitative measure of the uniformity of alveolar ventilation. Despite this, such measurements are useful clinically. With the continuous analysis method, they can be made rapidly and with a minimum of subject cooperation, and may be useful as a screening test for patients suspected of having abnormal pulmonary gas mixing.

SUMMARY

Continuous analyses were made of N_2 concentration and volume flow of gas expired after one inspiration of 99.6 per cent O_2. A ventilatory criterion for identifying alveolar gas is given. After O_2 inhalation, the N_2 concentration of

alveolar gas increased as expiration continued. During maximal ventilation the average increase in alveolar N_2 concentration was 5 per cent; the uniformity index was 0.725, which expresses the minimal variation in dilution of alveolar N_2 by inspired O_2. This finding indicates *a*) that inspired O_2 is not evenly distributed throughout the functional residual gas, and *b*) that the relatively poorly ventilated areas of the lung empty predominantly later in expiration. Uniform end-inspiratory distribution of inhaled O_2 is favored by larger inspired volumes and by breathholding. Uniformity of expired alveolar gas is affected by the rate and manner of expiration. The interpretation of data utilizing single alveolar gas samples is discussed.

Experimental evidence was obtained against the stratification theory of uneven lung ventilation and favoring the regional concept. A new concept, with supporting evidence, has been advanced to explain uneven ventilation on a temporal basis; this sequential ventilation results in a preferential distribution of the respiratory dead space gas to those regions which fill first on inspiration. Both preferential distribution of the dead space gas and also variations in percentage volume changes may occur as explanations for uneven alveolar ventilation.

Subjects with bronchial asthma and pulmonary emphysema showed greater variations in alveolar gas composition than did normal subjects. This difference makes the test useful in clinical diagnosis; measurements are made easily and rapidly. Their present limitations as a quantitative measure of intrapulmonary gas mixing are noted.

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Effect of Gas Density on Resistance to Respiratory Gas Flow in Man[1]

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RELIEF OF CERTAIN TYPES of dyspnea by substituting a mixture of helium and oxygen for air as the respired gas has been demonstrated by Barach (1, 2) and others (3–5). The beneficial effect is attributed to the fact that a smaller pressure gradient is required to move the less dense gas through a resistance (2). Dean and Visscher (6) by experiments on dog lungs have confirmed the belief that the apparent reduction in resistance to gas flow is related to the lesser density of the helium-oxygen mixture, and have further shown that it is actually due to a decreased turbulence. The relative ease of breathing which is subjectively noted at reduced barometric pressures (e.g. in a high altitude chamber) is presumably a similar phenomenon.

The purpose of this paper is to present data showing the magnitude of *the reduction in resistance to flow that occurs in the human respiratory tract* when the gas density is decreased by substituting helium-oxygen for air or by decreasing the barometric pressure, and to demonstrate that the observed decrease in resistance is adequately explained on the assumption that it is due to a decreased turbulence.

THEORETICAL

The pressure gradient required to move air in and out of the lungs is dependent on the geometry of the respiratory tract and on the density and viscosity of the respired gas. According to Rohrer (7) the relationship for the human respiratory tract between the volume-rate of flow and pressure gradient is $P = K_1V + K_2V^2$ where P is the pressure gradient and V the rate of flow. The validity of an equation of this form has been to some extent confirmed experimentally by Otis and Proctor (8). The linear part of the equation represents the stream-line flow component and its constant, K_1, includes the viscosity of the respired gas. The quadratic part represents the local turbulence occurring where the airways branch or suddenly change diameter, and its constant, K_2, includes the density of the air.

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Reduced barometric pressure or substitution of an 80 per cent helium–20 per cent oxygen mixture for air diminishes the density of the respired gas but alters the viscosity only slightly and should change the constant K_2 without greatly affecting K_1. (Both constants are dependent in part on the dimensions and configuration of the respiratory tract, but it seems reasonable to assume that these factors would be independent of the density of the gas breathed.)

EXPERIMENTAL

The alveolar pressure gradient and rate of flow were measured by the method previously described by Otis and Proctor (8) but with a somewhat more refined apparatus. The flow meter utilized 400-mesh monel gauze as a resistance. It had a dead space of only 70 cc., a resistance of 1 mm. H_2O/200 cc/sec., and gave linear calibration up to at least 4500 cc. per second. The interrupter was constructed in the form of a slide valve. It was closed by a solenoid magnet and returned to the open position by a counter-spring. Recording of the alveolar pressure and of the differential pressure from the flow meter was accomplished by means of strain gage pressure transmitters (Statham Laboratories) connected with a carrier wave amplifier which fed into the galvanometers of an oscillograph (Hathaway Instrument Co.).

For measurements of the effect of substituting helium-oxygen mixtures for air, the distal end of the flow-meter was connected to a set of inspiratory-expiratory valves. During the air-breathing period both valves were left open to the air on the side away from the subject. For the He-O_2 breathing period the inspiratory valve was switched to a spirometer containing 80 per cent helium–20 per cent oxygen. The general procedure was to record for about a minute with the subject breathing air, then to have the subject take several deep breaths of the He-O_2 mixture in order to flush the air out of the lungs, and finally to take a record with the subject breathing the mixture. During the periods of recording the subject was requested to breathe normally at first, then to increase his ventilation somewhat so as to obtain higher rates of flow.

In order to determine the effect of reduced barometric pressure, subjects were taken to the desired altitude in our low pressure chamber. Except during the actual measurements the subjects breathed oxygen from a demand system. When measurements were desired, the subject took a deep breath of oxygen, put on a nose clip, and then breathed from the mouth piece of the alveolar pressure apparatus. The distal end of the flow meter was, in these altitude experiments, connected to a 50-liter Douglas bag containing oxygen. Since only about a minute was required to obtain a set of measurements, the re-breathing that occurred with this arrangement was not excessive.

RESULTS

Comparison of Air and 80 Per Cent He–20 Per Cent O_2. The data obtained from measurements of the records taken on one individual are indicated by the points plotted in figure 1. Since our method shows no consistent difference between inspiratory and expiratory resistance to flow (8), no distinction has been made between points obtained during inspiration and those obtained during expiration. From inspection of the plotted points it is obvious that in general for a given rate of flow a smaller pressure gradient is required when helium–oxygen instead of air is the respired gas.

According to the theoretical discussion above, it should be possible to fit each of the two sets of data with a curve of the form given by *equation 1* in which K_1 should be approximately the same for both curves, but K_2 for air

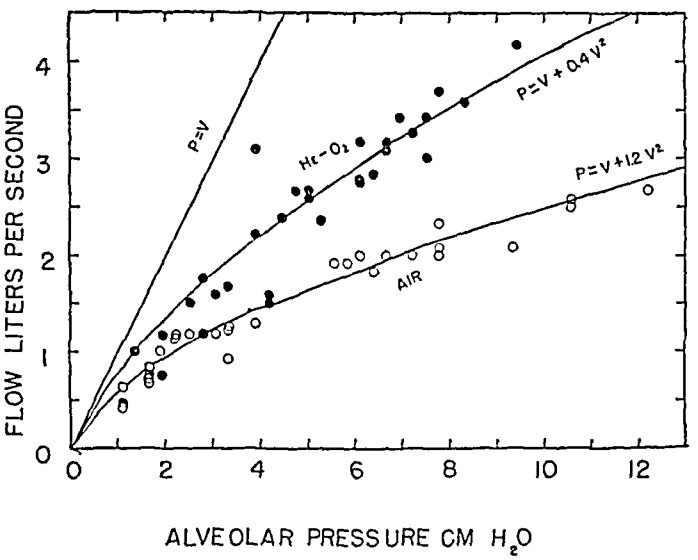

Fig. 1. Relationship between rate of flow and alveoli-mouth pressure gradient obtained for one subject, breathing air (open circles) and 80% He–20% O_2 (solid circles).

breathing should be about three times that for the helium-oxygen mixture, since the ratio of the density of air to that of a mixture of 80 per cent helium–20 per cent oxygen is approximately 3:1. Such a pair of curves have been constructed on figure 1, which seem to give a good fit to the experimental points. In addition, the straight line, $P = K_1V$, which represents the viscous flow component common to both gas mixtures, has been drawn. The distance along the abscissa from a chosen rate of flow on the axis of ordinates to this line represents the pressure required to overcome the viscous resistance for that rate of flow for either air or helium–oxygen. The additional distance that must be traversed along the same abscissa until the curve for $He–O_2$ is intercepted represents the additional pressure that must be developed to overcome the turbulence breathing this gas mixture. The pressure required to overcome turbulence for air breathing can be represented in a similar fashion.

Comparisons between air and 80 per cent helium–20 per cent oxygen as

the inspired gases were made on 20 individuals. In each case the data were graphed as in figure 1 and a free-hand curve was drawn through each set of plotted data. In each case the curve for the helium–oxygen lay above that for air. The points plotted in figure 2 are the means of the alveolar pressure values read off the individual curves of the 20 subjects at each of several rates of flow. These points have been fitted with curves of the form given by *equation 1* and in accordance with the theory discussed above. Although the fit of the curves to the points is not perfect, it is adequate as judged by the fact that the lines showing the extent of the standard error of the means which the points represent are intersected in all but one instance. It should be pointed out, however, the the deviation of the theoretical curves from the experimental

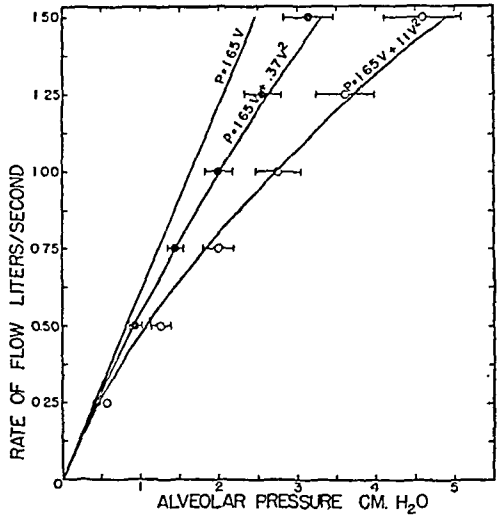

Fig. 2. RELATIONSHIP BETWEEN RATE OF FLOW and alveoli-mouth pressure gradient obtained for 20 subjects, breathing air (open circles) and breathing 80% He–20% O_2 (solid circles). Each point indicates the mean alveolar pressure of all subjects for a particular rate of flow. The horizontal lines through the points show the magnitude of the standard error of each mean.

points seems to be systematic rather than random. The nature of the discrepancy is such that it could be explained on the assumption that the airways offer relatively less resistance at the higher rates of flow. It may be that there is a mechanism whereby some parts of the respiratory tract become more dilated as the flow rate (or the pressure) increases. The glottis, for example, is capable of considerable variation in its aperture, and it is known to change rhythmically with the breathing cycle.

Comparison of Different Barometric Pressures. Measurements were made on 3 subjects at ground level and at the simulated altitudes of 18,000 and 36,000 feet. Figure 3 shows the results obtained at ground level and at 36,000 feet on one subject (the same subject is represented in fig. 1). The curves drawn on this graph were fitted according to the theory that the value for K_2 at 36,000 feet should be a little less than one-fourth that at ground level (ratio of the relative densities at the two altitudes).

The data from each of the 3 subjects at each of the three barometric pressures were grouped into class intervals according to velocity of flow, each

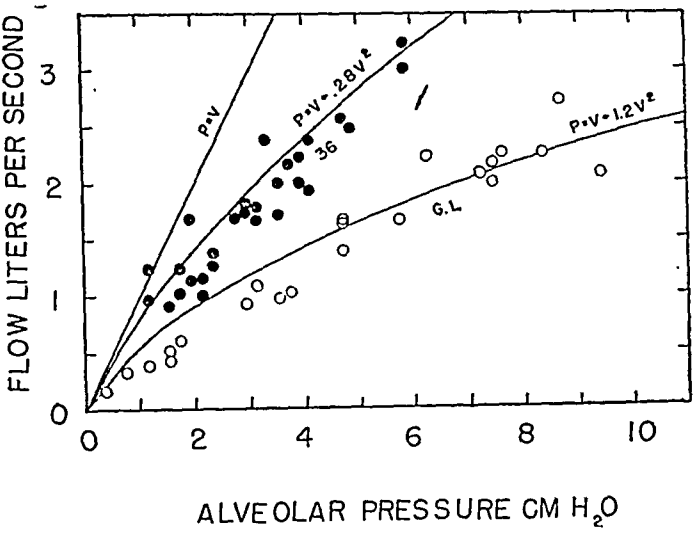

Fig. 3. RELATIONSHIP BETWEEN RATE OF FLOW and alveoli-mouth pressure gradient obtained for the same subject represented in figure 1, breathing O_2 at ground level (open circles) and at 36,000 feet (solid circles).

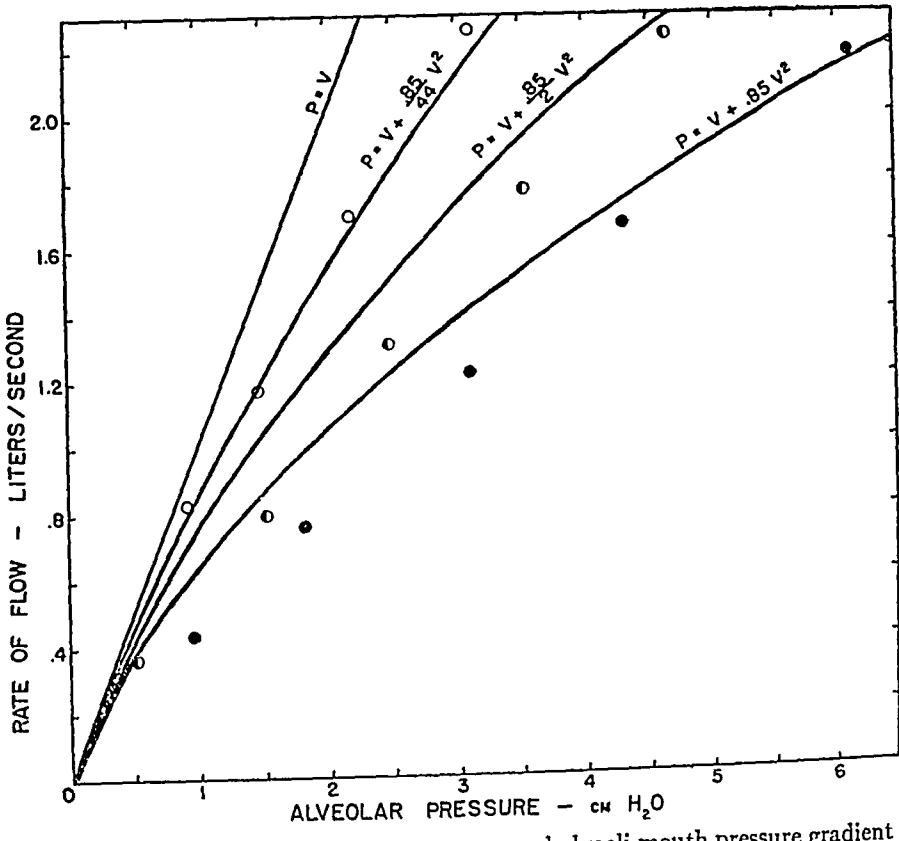

Fig. 4. RELATIONSHIP BETWEEN RATE OF FLOW and alveoli-mouth pressure gradient obtained for 3 individuals breathing oxygen at ground level (closed circles), and at 18,000 feet (half-open circles) and at 36,000 feet (open circles).

interval having a range of 500 cc/sec., and the mean alveolar pressure and mean velocity of flow were calculated for the values falling into each class in-

terval. The means from similar class intervals for the three subjects were averaged and the resulting grand means were plotted in figure 4. The curves in this figure were drawn according to the theory described above and seem to give an approximate fit, but show a deviation similar to that observed in the comparison between helium–oxygen and air.

COMMENT

It would be interesting to make similar measurements at pressures greater than atmospheric, but facilities for these were not readily available to us. However, by extrapolating the present data one can perhaps get a reasonable estimate of the alveolar pressures required under such conditions. For example, our average subject (fig. 2) developed an alveolar pressure of 2.75 cm. H_2O in moving air at 1 liter/second at ground level. At an environmental pressure of 4 atmospheres, as in diving, calculation shows that 6.05 cm. H_2O would be required for this rate of flow ($1.65 + (4 \times 1.1)$). Breathing at 2 liters/sec. would require 7.7 cm. H_2O at ground level, but 20.9 cm. H_2O at 4 atmospheres ($2 \times 1.65 + 4 \times 1.1 \times 2^2$).

Dr. Kenneth Donald (personal communication) states that at a pressure of 8 atmospheres the turbulence is so great that one can actually feel eddy currents in the air as it flows through the mouth. At this barometric pressure the gradient required to respire at a rate of 2 liters/second would be 38.5 cm. H_2O according to our extrapolation. On the other hand, breathing at this velocity at an altitude of 46,000 feet would require only about 4 cm. H_2O.

In making the theoretical calculations in this paper we have assumed that helium–oxygen has the same viscosity as air (actually the viscosity of helium is about 10 per cent greater than that of nitrogen). The effect of carbon dioxide and water vapor on the viscosity and density of the respired gas has also been neglected. We feel that the error in these approximations is less than that in the actual measurements of the alveolar pressures and rates of flow.

SUMMARY

The alveolar pressures required to produce various velocities of respiratory gas flow have been measured in 20 human subjects breathing 1) air and 2) 80 per cent helium–20 per cent oxygen. In 3 subjects a similar comparison has been made between air breathing at ground level and at simulated altitudes of 18,000 and 36,000 feet. Less alveolar pressure is required to produce a given velocity of flow when a person breathes 80 per cent helium–20 per cent oxygen at ground level or air at altitude than when he breathes air at ground level. Theoretical treatment of the data indicates that this effect is due to a decreased turbulence in the less dense gases. The data also suggest that some parts of the respiratory tract may dilate when one breathes at high velocities.

We thank Dr. Wallace O. Fenn and Dr. Hermann Rahn for helpful suggestions and for participation in some of the experiments and Miss Helen Jacobs for technical assistance.

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Measurement of Saturation Time and Saturation Tension with Millikan Oximeter, in Subjects with Normal Pulmonary Function[1]

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THE OXYGEN SATURATION of the mixed arterial blood (i.e., blood in the left heart and systemic arteries, in which fractions of blood from all portions of the lung are pooled and have come into equilibrium with each other) may be considered to reflect the state of pulmonary function. Adequate pulmonary function—the satisfactory performance of external respiration—depends on two main factors, ventilation and diffusion. The efficiency of ventilation of individual alveoli probably varies considerably even in the normal lung. Paul and Ferguson (1) have used the term 'alveolar inhomogeneity' to describe the variation in gas tensions in different areas of the lung, whereas Lilienthal *et al.* (2) employ the phrase 'varying distribution' to describe essentially the same phenomenon. The consequence of this inhomogeneity will be that blood from different areas of lung will have varying degrees of oxygen saturation. The efficiency of gas exchange will also be affected by the ease with which diffusion is accomplished across the tissue-fluid barrier separating alveolar contents and the hemoglobin of the red cell (2). An increase in the resistance offered by this barrier will result in a greater drop in pO_2 from alveolus to capillary and a lesser degree of oxygen saturation of arterial blood.

The development in recent years of instruments such as the Millikan oximeter (3) has made it possible to observe the arterial oxygen saturation continuously. In this paper, the changes in arterial oxygen saturation found with variations in the inspired oxygen tension are reported, as recorded by the oximeter. In particular, determinations have been made of the oxygen tension of the inspired air required to saturate the mixed arterial blood 99.5 per cent and of the time required to reach full saturation when breathing pure oxygen.

METHODS

Blood Gas Analysis. Blood samples were analyzed using the Van Slyke-Neill manometric apparatus. Samples were collected by the method of Gold-

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[2] Fellow of the National Research Council of Canada.

schmidt and Light (4), drawing venous blood anaerobically from a dorsal vein of the hand, after immersion of the hand to the wrist in water at 45°–47°C. for 10 minutes.

Determinations of oxygen capacity were made by equilibrating a sample of blood in a rotating flask with fifty times its volume of room air. The results were multiplied by 0.98, as Roughton *et al.* (5) have shown that various errors in the method of equilibration give a value for capacity approximately 2 per cent too high. Corrections for dissolved oxygen were made using the nomogram of Sendroy *et al.* (6).

From the oxygen content of samples of arterialized-venous blood, drawn while the subject breathed pure oxygen, a correction of 1.96 volumes per cent was subtracted for oxygen dissolved in whole blood. Recently Wood (7) has suggested that this correction should be 1.83 volumes per cent. The correction used was based on an alveolar pO_2 of 657 mm. Hg, an alveolar-arterial pO_2 gradient of 11 mm. Hg (8), and a coefficient of solubility for oxygen in whole blood of 0.023 (6). For example:

(Alveolar pO_2 on 100% O_2) − (Alveolar-Arterial pO_2 Gradient) = Arterial pO_2

657 mm. Hg − 11 mm. Hg = 646 mm. Hg

$$\text{Oxygen dissolved in whole blood} = \frac{646 \text{ mm. Hg}}{760 \text{ mm. Hg}} \times 0.023 = 1.96 \text{ vol. \%}$$

If the corrected value for oxygen content equalled the corrected value for oxygen capacity, the sample of blood was considered to be saturated completely.

Measurement of Arterial Oxygen Saturation on Ambient Air. The Millikan oximeter (single channel compensated oximeter, C.M.R. *Model 13*) (3) was used to measure arterial oxygen saturation on ambient air. The oximeter has no absolute accuracy, but measures variations in saturation from some pre-set value. The subject breathed 100 per cent oxygen for ten minutes and a sample of arterialized-venous blood was collected at the end of this time. If analysis showed that the blood was completely saturated, then the oximeter could subsequently be set at 100 per cent saturation when the subject breathed pure oxygen.

Determinations of arterial oxygen saturation with the subject breathing air were made by setting the oximeter at 100 per cent saturation after 10 minutes of pure oxygen breathing, and then noting the oximeter reading with the subject breathing air, after the reading had fallen to a new steady level.

Determination of Alveolar Oxygen Concentration Required to Produce 99.5 Per Cent Saturation (Saturation Tension). For this measurement, the oximeter was used as a null instrument to indicate arrival at and departure from complete saturation. The subject was semi-recumbent on a couch with a raised

back-rest, the legs making an angle of 110° with the trunk. Two measurements were taken—'ascending' and 'descending'—on subjects previously proven to attain complete arterial oxygen saturation on pure oxygen by blood gas analysis.

Descending Measurement. After the subject had breathed 100 per cent oxygen for 10 minutes from a nine-liter Collins' spirometer in a closed rebreathing circuit equipped with a blower and a CO_2 absorber, with several washouts of the system with oxygen, the oximeter was set at 100 per cent saturation. Then approximately 4 liters of nitrogen were added to the spirometer and the subject continued to rebreathe the mixture, absorbing oxygen and thus gradually reducing the oxygen concentration of the mixture, until the arterial saturation, as indicated by the oximeter, fell to 99.0 per cent. When this occurred, samples of alveolar air (Haldane-Priestley method) and of the inspired gas mixture were taken for analysis in the Haldane-Henderson apparatus.

Ascending Measurement. The subject began rebreathing from the spirometer system now filled with air, arterial saturation by oximeter falling to about 96 per cent. Oxygen was then added to the system at the rate of 150 cc. per minute in excess of absorption, amounting to an increase of approximately 1 per cent per minute in the oxygen concentration of the chest-spirometer system. Readings of saturation were taken at one-minute intervals until there had been no further increase in saturation on four successive readings. Then samples of alveolar and inspired air were again taken for analysis.

Determination of 'Saturation Time.' Using the oximeter as an indicator of arterial oxygen saturation, the time required to reach complete saturation, when the subject changed from breathing air to pure oxygen, was determined. The change from breathing ambient air to oxygen was accomplished by placing an R.C.A.F. type C_3 oxygen mask, connected through a demand valve to a tank of oxygen. Timing was begun with the first 'hiss' of the demand valve, which marked the first inspiration of pure oxygen. The dead space of the tubing and the mask had previously been washed out with oxygen.

The method described by Fowler and Comroe (9) was used and saturation was noted from the oximeter at 5-second intervals up to 75 seconds, and then at 15-second intervals until no further rise had occurred for at least one minute. Using this final value of the oximeter reading as 100 per cent saturation, the time which had been required to reach 99.5 per cent saturation was calculated and this was taken as the saturation time.

Since saturation plotted against time appeared to increase in an exponential type of curve when the subject changed from breathing ambient air to oxygen, after an initial delay, it was considered that the slope or half-time of a straight line obtained by plotting saturation against time on semi-logarithmic paper might give a better expression of the rate of saturation increase.

It was found that, after the initial pause, the increase in saturation plotted against time on semi-logarithmic paper was approximately linear up to 99.5 per cent saturation, when it usually fell away to the right. The best line was drawn through the straightest part of this curve, and the half-time of this line was determined.

TABLE 1. ARTERIAL OXYGEN SATURATION IN FORTY-SIX SUBJECTS WITH NORMAL PULMONARY FUNCTION, BREATHING 100 PER CENT OXYGEN

CASE NO.	O_2 CONTENT ON 100% O_2	O_2 CAPACITY	OXYGEN SATURATION	CASE NO.	O_2 CONTENT ON 100% O_2	O_2 CAPACITY	OXYGEN SATURATION
	vol.%[1]	*vol.%*[2]	%		*vol.%*[1]	*vol.%*[2]	%
1	19.80	19.70	100.5	*24*	19.88	19.47	102.0
2	20.00	20.00	100.0	*25*	20.10	19.83	101.3
3	20.34	20.19	100.8	*26*	20.85	21.08	98.9
4	21.52	21.51	100.0	*27*	20.02	20.35	98.4
5	20.80	20.93	99.4	*28*	20.28	20.27	100.0
6	21.23	21.20	100.2	*29*	20.31	20.14	100.8
7	20.79	20.66	100.5	*30*	18.58	18.76	99.0
8	21.90	21.95	99.7	*31*	20.59	20.80	98.9
9	19.91	19.98	99.6	*32*	19.90	19.83	100.4
10	20.59	20.47	100.5	*33*	19.44	19.28	100.8
11	21.42	21.30	100.5	*34*	19.83	19.93	99.5
12	20.79	20.87	99.6	*35*	20.41	20.38	100.1
13	20.57	20.55	100.0	*36*	19.81	19.87	99.7
14	20.46	20.38	100.4	*37*	21.35	20.83	102.5
15	22.25	22.19	100.3	*38*	22.47	22.88	98.2
16	18.05	18.39	98.5	*39*	17.74	17.81	99.6
17	18.22	18.20	100.1	*40*	20.01	19.93	100.4
18	19.02	18.80	101.1	*41*	18.68	18.86	99.0
19	20.90	21.05	99.3	*42*	21.80	21.56	101.1
20	21.99	21.75	101.3	*43*	21.66	21.60	100.3
21	16.72	16.75	99.6	*44*	17.93	17.98	99.7
22	20.37	20.15	101.3	*45*	22.34	22.30	100.2
23	19.76	20.05	98.6	*46*	19.85	19.81	100.2

Mean arterial oxygen saturation: 100.1 ± 0.7% Range: 98.2–102.5%.

[1] Corrected for dissolved oxygen by subtracting 1.96 vol. %.

[2] Corrected by subtracting dissolved oxygen calculated by using the nomogram of Sendroy *et al.* and multiplying the result by 0.98 for equilibration errors.

MATERIAL

Forty-six subjects without pulmonary disease were examined, ranging in age from 22 to 71 years. All but two of these were males. The assumption that their pulmonary function was normal was based on history, physical examination, chest x-ray and response to exercise.

RESULTS

Arterial Oxygen Saturation on 100 Per Cent Oxygen. Using the method of calculation outlined above, the mean oxygen saturation of 46 normal subjects

breathing 100 per cent oxygen was found to be 100.1 ± 0.7 per cent, with a range of from 98.2 to 102.5 per cent (arterialized-venous blood) (table 1).

Measurement of Arterial Oxygen Saturation Breathing Air (Oximeter). In 46 normal subjects, the mean value for saturation when breathing air was 96.2 ± 0.2 per cent, as measured by the oximeter. Values ranged from 93.5 to 97.5 per cent (fig. 1).

Measurement of Saturation Tension. The results of this measurement in 39 normale subjcts, ranging in age from 22 to 39 years, are summarized in

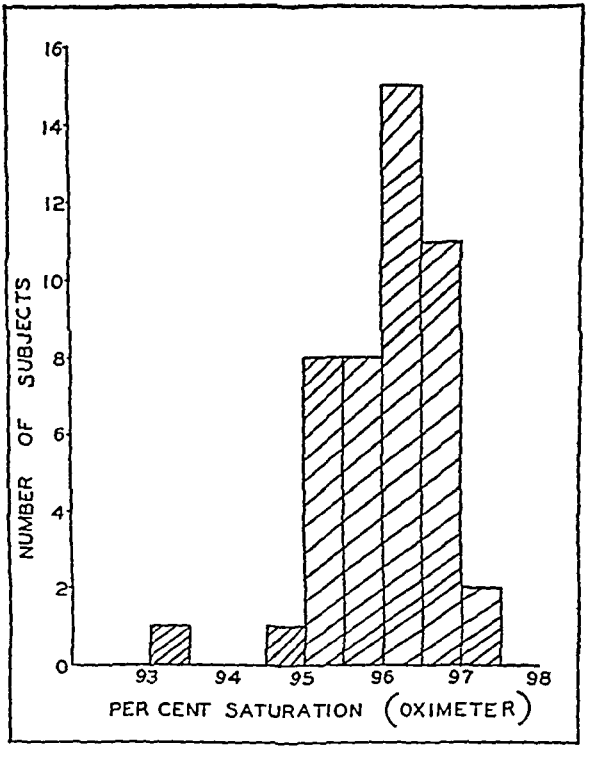

Fig. 1. DISTRIBUTION OF ARTERIAL OXYGEN saturation values obtained by oximeter in 46 normal subjects breathing air.

table 2, which shows the 'ascending' and 'descending' alveolar and inspired (spirometer) pO_2's required to produce 100 per cent and 99 per cent oxygen saturation of the arterial blood as measured by the oximeter. Owing to errors in measurement, it is probable that both measurements overshoot the true value, so the mean of the ascending and descending measurements has been taken as the significant value, and has been arbitrarily considered to represent 99.5 per cent saturation. The mean alveolar pO_2 required to produce 99.5 per cent saturation is 212.9 ± 7.7 mm. Hg, and the mean spirometer pO_2 261.3 ± 8.9 mm. Hg, or approximately 35 per cent oxygen.

Age may affect these measurements. Table 3 shows the increase in saturation tension found in the small number of normal subjects 40 years of age or older examined. No significant difference in saturation tension was found between the group 29 years of age or younger and the group between 30 and 39 years inclusive.

Measurement of Saturation Time. In 46 normal subjects the mean saturation time, measured to 99.5 per cent saturation, was 58.4 ± 6.1 seconds, with a range of from 42 to 71 seconds. The mean saturation half-time in the same subjects equalled 17.3 ± 1.6 seconds, with a range of from 13 to 20 seconds. No increase in saturation time was found in the subjects 40 years of age or older. The increase of saturation plotted against time on semi-logarithmic

TABLE 2. SATURATION TENSION IN THIRTY-NINE NORMAL SUBJECTS RANGING IN AGE FROM TWENTY-TWO TO THIRTY-NINE YEARS

MEASUREMENT	SPIROMETER pO_2 *mm. Hg*				ALVEOLAR pO_2 *mm. Hg*			
	Mean	S.D.	S.E.M.	Range	Mean	S.D.	S.E.M.	Range
Decending.....	239.6	11.3	1.8	211–260	189.9	9.6	1.6	169–216
Ascending.....	282.4	9.6	1.5	259–305	231.7	9.1	1.5	212–251
Mean.....	261.3	8.9	1.4	240–282	212.9	7.7	1.2	193–230

Average age: 28 yrs.

TABLE 3. SATURATION TENSION IN FORTY-SIX NORMAL SUBJECTS, SUBDIVIDED ACCORDING TO AGE

AGE	20–29	30–39	40–71
No. of cases.....	30	9	7
Mean spirometer pO_2.....	260.7	263.3	290.0
Mean alveolar pO_2.....	211.8	216.6	245.0

paper is shown in figure 2. No significant correlation was found between saturation tension and saturation half-time ($r = +0.06 \pm 0.16$) or between saturation tension and saturation time measured to 99.5 per cent saturation ($r = +0.14 \pm 0.20$) in the same subject. However, a significant correlation did exist between measurements of saturation time by the two methods, the coefficient of correlation being $+0.63 \pm 0.18$.

DISCUSSION

The accuracy of the Millikan oximeter in the measurement of arterial oxygen saturation has been criticized. Millikan's estimate of its accuracy in high saturation ranges was ±5 per cent saturation (3). Sleator *et al.* (10) have suggested that the capillary blood passing in front of the photo-cells of the oximeter earpiece may not be completely 'arterialized,' and may contain venous components draining from unheated portions of the ear. Hemingway and Taylor (11) have pointed out that absolute agreement between oximeter satura-

tion values and those obtained by blood gas analysis with the Van Slyke-Neil apparatus is impossible due to the inherent errors of each instrument. Geraci *et al.* have carried out extensive calibrations of individual Millikan earpieces with the revelation of considerable discrepancies (12). In the present work, the oximeter has been used as a reading instrument only for the determination of saturation on ambient air, and the average value obtained (96.2%) has been in close agreement with that found by others using the oximeter (13), although

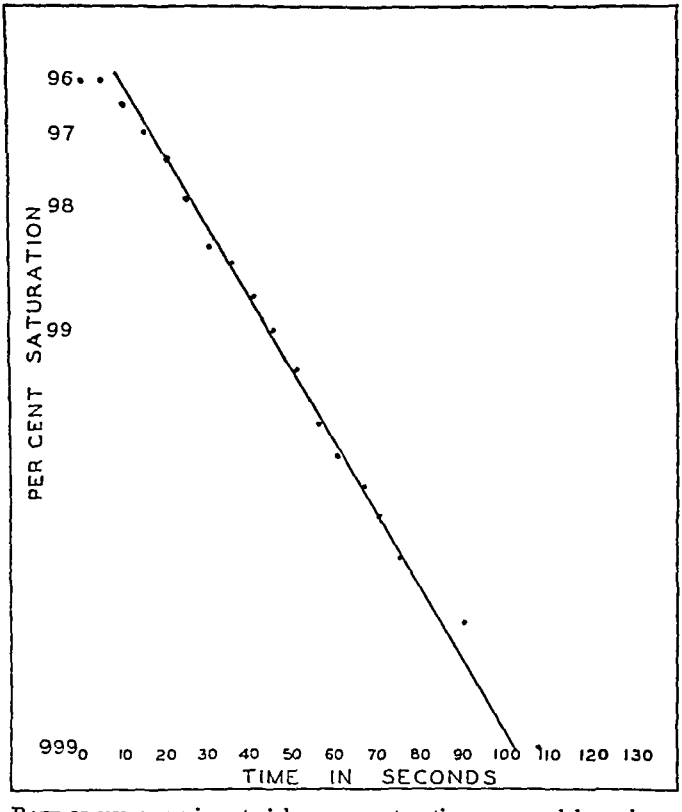

Fig. 2. RATE OF INCREASE in arterial oxygen saturation measured by oximeter in a normal subject, after commencement of pure oxygen breathing (plotted on semi-logarithmic paper).

values obtained for saturation on air recently by other methods have been higher (5, 7)

In the measurement of both saturation tension and saturation time, the point read was one relatively unaffected by the errors of the instrument. Saturation tension was measured by using the instrument essentially as a null instrument to indicate arrival at, or departure from, a known point, i.e. with the subject breathing 100 per cent oxygen, the oximeter had been set at 100 per cent saturation. In the case of saturation time, the oximeter was used to measure the rate of rise to maximum saturation, regardless of the final scale

reading. It is believed that the shortcomings of the oximeter were minimized by its use in this manner. These measurements (saturation tension and saturation time) vary only slightly from one individual to another in the case of normal subjects, as shown by the small standard deviation.

Fowler and Comroe (9) have pointed out that the oximeter saturation reading will show a further slight rise if the oxygen concentration in the inspired air is increased beyond 40 per cent. We have been able to reproduce these results. This finding may seem to cast doubt on the validity of our 'ascending' measurement of saturation tension, but as previously noted the end-point used was chosen for convenience in reading and was consistent in the same subject.

The increase in oxygen concentration inspired over that of air (to approximately 35%) required to produce 99.5 per cent saturation as shown by the oximeter may seem surprisingly great, since arterial blood is almost completely saturated when a normal subject is breathing air. No dissociation curve for oxygen under *in vivo* conditions has yet been constructed beyond a saturation of 98 per cent. The oxygen dissociation curve constructed by Riley *et al.* (14) indicates a saturation of 98 per cent at a pO_2 of 113 mm. Hg with a p_H of 7.4 and a temperature of 37°C. Our work indicates that a pO_2 of approximately 200 mm. Hg in arterial blood is required to raise saturation to 99.5 per cent. However, in addition to blood which has perfused ideally ventilated alveoli, there are components from less well-ventilated alveoli, and finally elements of frank venous blood (from bronchial veins, thebesian vessels, etc.) are added which must be saturated by an excess of plasma dissolved oxygen from blood in contact with well-ventilated alveoli. With the hemoglobin fully saturated, a great increase in pO_2 is required to effect a slight increase in the quantity of oxygen carried per cubic centimeter of whole blood, for any gain will be in dissolved oxygen of necessity, and the coefficient of solubility for oxygen in whole blood is low. Thus a small amount of venous blood may be expected to cause a disproportionately large increase in the inspired oxygen concentration required for 'complete' (99.5%) saturation of mixed arterial blood.

The measurements of the time required to reach 100 per cent minus 0.5 per cent saturation (saturation time) are not significantly different from those obtained by Fowler and Comroe (9). As these authors have pointed out, a large part of the approximately 60 seconds involved remains unexplained, since a few breaths of pure oxygen should raise the alveolar pO_2 to levels of at least 240 mm. Hg, and lung-to-ear circulation time amounts to only a few seconds. Here again venous admixture, both in the mixed arterial blood and perhaps also in the 'arterialized' capillary blood in front of the photocells, may account for the discrepancy (10). Moreover, Burton (15) has pointed out that the equilibrium between streams of blood derived from segments of lung with

different oxygen tensions is slowly accomplished when these fractions are pooled in the systemic circulation, due to the slow rate of diffusion of oxygen in liquids. However, the measurement of Saturation Tension has also been reproducible within significant limits in normal subjects.

Considering the interpretation of the two measurements, saturation tension may be expected to be sensitive to venous additions to the mixed arterial blood from any cause—underventilation of alveoli or circulation of blood through portions of lung with an increased resistance to diffusion between the alveolar gas and capillary blood. Saturation time, on the other hand, would be influenced by all the factors affecting the mixed arterial saturation, including those mentioned above. It is probably chiefly influenced by the efficiency of intrapulmonary mixing of gases. The lack of significant correlation ($r = +0.14 \pm 0.20$) between measurements of saturation time and saturation tension in normal subjects suggests that the factors influencing these two measurements are either not the same or, more probably, are weighted differently.

SUMMARY AND CONCLUSIONS

Saturation time and saturation tension are two simple measurements of the subject's behavior with regard to mixed arterial oxygen saturation under varying conditions of inspired oxygen concentration. In 46 subjects free from perceptible pulmonary damage, and ranging in age from 22 to 71 years, the results obtained for these measurements were significantly consistent and there is evidence that saturation tension increases with advancing age.

The oxygen saturation of the mixed arterial blood may be considered to reflect the state of pulmonary function, when considered under varying conditions of inspired oxygen concentration. Using the Millikan Oximeter as an indicator of arterial oxygen saturation, a study has been made of the increase in pO_2 of the inspired gas mixture required to raise saturation to a given level (e.g., 99.5%) from its level of 95 to 97 per cent when the subject breathes room air. In normal subjects, an alveolar oxygen tension of 212.9 ± 7.7 mm. Hg produces 99.5 per cent saturation. This corresponds to an average inspired pO_2 of 261.3 ± 8.9 mm. Hg, or approximately 35 per cent oxygen. (These figures represent the mean of the 'ascending' and 'descending' measurements.) The time required to reach complete saturation when the subject changes from breathing room air to pure oxygen has also been determined. This, expressed as time to maximum saturation minus 0.5 per cent, has been found to equal 58.4 ± 6.1 seconds in a series of normal subjects. Expressed as half-time, it has been found to equal 17.3 ± 1.6 seconds.

We wish to acknowledge the valuable suggestions and criticism of Dr. A. C. Burton.

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Effect of Change of Position upon the Cerebral Circulation of Man[1,2]

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THE INTRINSIC CONTROL of the cerebral circulation has been the subject of study chiefly in the experimental animal, generally under the influence of anesthesia. These studies, further, have usually been hampered by the lack of quantitative methods for the measurement of the cerebral blood flow. These investigations have demonstrated a neurogenic mechanism for cerebral vasoconstriction and vasodilatation. The neurogenic control, however, is generally considered to be heavily outweighed by a chemical control chiefly expressed by a tonic dilatation of vessels with an intrinsically high tone (1).

The introduction by Kety and Schmidt (2) of a quantitative method for study of the cerebral blood flow, applicable to humans in the unanesthetized state, offered us the opportunity of studying the intrinsic control of the cerebral circulation, eliminating the problem of species differences and permitting a quantitative correlation of the various physiologic factors involved. It was felt that the study of the cerebral circulation with change of position from the horizontal might elicit normal homeostatic mechanisms as well as offer practical conclusions as to the therapeutic utility of these positions.

METHODS

The cerebral blood flow was determined by the nitrous oxide method of Kety (2). The subjects were of two types. The first group was made up of psychoneurotic individuals or patients with mild idiopathic epilepsy, none of whom had evidence of physiological changes on physical examination and after a thorough neurological study. This group, it was felt, with certain reservations, would reflect the physiological reactions of normal individuals to change of position. The second group of patients studied had increased intracranial pressure, the result of brain tumor. Both groups were studied in an identical

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manner. A resting cerebral blood flow was obtained with the patient in the horizontal, supine position. Five minutes after the end of the first (or control) cerebral blood flow study, the patients were tilted 20°, some head up and some head down. After being in a tilted position for 10 minutes a second blood flow study was done. The 20° tilt position was selected since this was about the height to which patients are raised in bed post-operatively in many neurosurgical clinics.

The mean arterial pressure was obtained directly from the femoral artery by means of a damped mercurial manometer. The mean blood pressure in the carotid vessels with the patient tilted was estimated by appropriate correction of the femoral blood pressure. The correction was derived from the distance between the carotid bifurcation and the needle in the femoral vessel multiplied by the sine of the angle of tilt.

The cerebrospinal fluid pressure was measured with the patient horizontal and on his side using a water manometer attached to a needle inserted into the lumbar subarachnoid space. The intracranial cerebrospinal fluid pressure in the tilted position was calculated in the normal series by an appropriate correction derived from the distance between the occiput and the needle in the lumbar sac multiplied by the sine of the angle of tilt. This was not done in each of the experiments reported here. However, we have measured the lumbar spinal fluid pressure in the 20° tilted position both up and down in a series of 10 relatively normal patients. Calculating the intracranial pressure from this data as suggested by Kunkle, Ray and Wolff (3) only small deviations from the mean change of 142 mm. H_2O to be subtracted from the prone lumbar sac pressure in the 20° head-up position and 153 mm. H_2O to be added in the 20° head-down position were found. This average change was added to, or subtracted from, the prone lumbar spinal fluid pressure of the patients in this series to approximate the intracranial pressure in the 20° head-up or head-down position. The spinal fluid pressure was also measured in the tilted position in a group of patients with increased intracranial pressure due to brain tumor. The deviations from the average, however, were so large and inconsistent that it was not felt to be justifiable to draw any conclusions with regard to the intracranial pressure in the tilted position in the series of increased intracranial pressure patients reported in this paper.

Blood O_2 and CO_2 analyses were made by the manometric technique of Van Slyke and Neill (4). Blood *p*H measurements were made anerobically at 37° C. using a glass electrode. The CO_2 tension was calculated by means of the nomograms of Peters and Van Slyke.

Cerebral oxygen consumption was calculated by multiplying the arteriovenous oxygen difference by the cerebral blood flow and the cerebrovascular resistance (CVR) was determined by dividing the mean arterial blood pressure by the cerebral blood flow (2). While a true value for cerebrovascular resistance

would require the gradient of pressure across the brain obtained by subtracting the internal jugular pressure from the carotid pressure, we have found the changes in jugular pressure with a 20° tilt to be only in the range of 1 to 2 mm. Hg. This change would not influence the relative values for cerebrovascular resistance and in the majority of the experiments only the mean carotid pressure has been utilized in calculating the cerebrovascular resistance.

RESULTS

Tables 1 and 2 summarize the entire data. No significant change of the cerebral blood flow was recorded in a group of 5 physiologically normal individuals when tilted head up 20° from the horizontal. There was, of course, a significant lowering of the mean carotid pressure, from an average of 88 to 73 mm. Hg (a 17% decrease) and a lowering of the intracranial cerebrospinal fluid pressure from 133 mm. of water to −9 mm. The maintenance of the cerebral blood flow in the face of this drop in pressure was explained by a fall in the cerebrovascular resistance (averaging 18%). A significant rise in venous CO_2 tension was also recorded. There was no real change in the cerebral oxygen consumption or in the arteriovenous oxygen difference.

In a group of 6 patients with brain tumor, 5 had increased intracranial pressure and one had no increase in pressure but was semicomatose. These patients when tilted head up 20° had a distinct fall (30%) in C.B.F., from an average of 51 to 36 cc/100g/min. There was no change, however, in the cerebral oxygen consumption despite the marked change in the arteriovenous oxygen difference (from a mean of 5.6 to 7.0 vol. %). The mean carotid pressure dropped from an average of 92 to 86 mm. Hg and the cerebrovascular resistance increased by 25 per cent. The fall in carotid blood pressure averaged only 6 per cent as compared with 17 per cent in the more normal group when tilted head up. There were no changes in any of the blood gas values.

Four probably neurotic but otherwise physiologically normal individuals were tilted head down 20° from the horizontal. There was a consistent fall in C.B.F. from an average of 61 to 52 cc/100g/min. (14%). This was accompanied by a decrease in cerebral oxygen consumption averaging 18 per cent. There was no consistent change in arteriovenous oxygen difference in this group. The mean carotid pressure increased significantly with this maneuver, averaging 10 per cent and the calculated intracranial cerebrospinal fluid pressure increased on the average from 137 mm. of water to 290 mm. This was accompanied by an increase in cerebrovascular resistance averaging 24 per cent, well explaining the fall in cerebral blood flow in the head-down position. A significant change also recorded was a fall in venous carbon dioxide content averaging 1.3 volumes per cent. A consistent fall in the arterial oxygen content averaging 0.6 volume per cent was found, but in this group alone it was not statistically significant. However, when utilizing the entire series of patients tilted head

TABLE 1. BLOOD GASES AND CEREBRAL CIRCULATION AND METABOLISM BEFORE (I) AND AFTER (II) A 20° TILT HEAD UP IN PHYSIOLOGICALLY NORMAL PATIENTS AND PATIENTS WITH BRAIN TUMOR

SUBJECT	AGE	INTERNAL JUGULAR				ARTERIAL				CEREBRAL											
		O_2 Content		CO_2 Content		O_2 Content		CO_2 Content		O_2		C.B.F.		$CMRO_2$		C.V.R.		M.C.P.		C.F.P.	
		Vol. %		*Vol. %*		*Vol. %*		*Vol. %*		*Vol. %*		*cc/100g/min.*		*cc/100g/min.*		*mm. Hg cc/100g/min.*		*mm. Hg*		*mm. H₂O*	
		I	II	I	II	I	II	I	II	I	II	I	II	I	II	I	II	I	II	I	II
Normals																					
E. B.	27	10.8	10.4	52.0	54.3	17.3	17.6	46.3	48.3	6.5	7.2	56	52	3.6	3.7	1.5	1.3	84	64	160	18
S. W.	37	10.1	11.8	56.4	56.7	17.9	19.1	48.1	49.4	7.8	7.3	46	48	3.6	3.5	1.8	1.7	84	74	120	−22
J.C.	31	10.8	10.7	49.2	50.3	17.4	16.9	43.5	43.6	6.6	6.2	49	52	3.2	3.2	2.0	1.4	96	73	160	18
R.P.	32	10.1	9.7	46.9	47.7	16.0	16.1	41.8	41.4	5.9	6.4	62	59	3.7	3.7	1.3	1.1	82	66	90	−52
M.M.	42	9.8	9.6	54.0	54.8	13.4	13.8	49.0	50.6	3.6	4.3	52	60	1.9	2.6	1.8	1.5	96	90	130	−12
Mean	34	10.3	10.4	51.7	52.8[1]	16.4	16.7	45.7	46.7	6.1	6.3	53	54	3.2	3.3	1.7	1.4[1]	88	73[1]	133	−9
Brain Tumor Patients																					
D.L.	61	11.7	11.5	74.4	74.0	18.1	18.4	68.4	65.5	6.4	6.9	42	29	2.8	2.0	2.6	3.8	109	109	135	
L.S.	57	7.7	7.6	52.5	51.5	14.9	14.9	44.3	43.5	7.2	7.3	45	36	3.2	2.6	1.8	1.9	80	69	230	
J.B.	33	10.5	8.8	54.5	56.5	17.4	17.0	49.3	49.8	6.9	8.2	47	43	3.2	3.5	2.2	2.3	104	100	250	
W.W.	48	13.7	9.2	56.5	56.5	16.2	14.9	53.9	52.4	2.5	5.7	94	41	2.3	2.3	1.1	2.2	98	91	250	
E.W.	44	9.3	7.6	54.5	55.8	14.3	14.6	49.6	49.2	5.0	7.0	40	36	2.0	2.5	2.2	2.1	87	77	350	
J.D.	38	10.3		50.0			16.5		37.7			37	28			2.0	2.4	74	67	250	
Mean	47	10.5	8.9	58.5	58.9	16.2	16.1	53.1	49.7	5.6	7.0[1]	51	36[1]	2.7	2.6	2.0	2.5[1]	92	86[1]	244	
Total mean.	41	10.4	9.7	54.7	55.9	16.3	16.3	49.4	48.3	5.8	6.7[1]	52	44	3.0	3.0	1.8	2.0	90	80[1]	193	

$C.B.F.O_2$ = Cerebral blood flow. $CMRO_2$ = Cerebral metabolic rate (oxygen consumption). C.V.R. = Cerebrovascular resistance. M.C.P. = Mean carotid pressure. C.F.P. = Calculated intracranial cerebrospinal fluid pressurre.

[1] Denotes a siguificant change.

TABLE 2. BLOOD GASES AND CEREBRAL CIRCULATION AND METABOLISM BEFORE (I) AND AFTER (II) A 20° TILT HEAD DOWN IN PHYSIOLOGICALLY NORMAL PATIENTS AND PATIENTS WITH BRAIN TUMOR

SUBJECT	AGE	INTERNAL JUGULAR				ARTERIAL				CEREBRAL											
		O_2 Content		CO_2 Content		O_2 Content		CO_2 Content		A-V_{O_2}		C B F.		CMR_{O_2}		C.V.R.		M.C.P.		C.F.P.	
		Vol. %		*Vol. %*		*Vol %*		*Vol %*		*Vol. %*		*cc/100 g / min*		*cc/100 g/min.*		*mm Hg cc/100 g/min.*		*mm. Hg*		*mm H_2O*	
		I	II	I	II	I	II	I	II	I	II	I	II	I	II	I	II	I	II	I	II
Normals																					
J S.	20	11.4	11.5	55.1	54.0	18.7	18.0	46 8	47.6	7.3	6.5	58	45	4.2	2.9	1.5	2.2	87	100	400	293
M.H.	33	9.6	8.8	52.9	50.4	17.8	17.7	45 7	42.5	8.2	8.9	68	57	5.6	5.1	1.4	1.8	96	105	150	303
G W.	52	10.1	9.6	55.2	54 4	14.6	14.0	51 0	50.2	4.5	4.4	72	63	3.2	2.8	1.6	2.0	117	124	120	273
R.P.	21	12.1	12.2	52.3	51.5[1]	18.0	17 0	46 8	47.8	5 9	4.8	45	41	2.7	2.0	2.1	2.5	93	104	130	283
Mean .	32	10.8	10.5	53.9	52.6*	17.3	16.7	47.6	47.0	6.5	6.2	61	52[1]	3.9	3.2[1]	1.7	2.1[1]	98	108[1]	135	290
Brain Tumor Patients																					
L.W.	38	9.4	9.8	52.1	53.0	17.4	17.0	44.6	46.7	8.0	7.2	42	41	3.4	3.0	2.7	2.9	114	117	400	
G.C.	22	10.4	12.2	52.9	51.3	18.2	18 0	45 7	45.0	7.8	5.8	60	59	4.7	3.4	1.5	1.6	91	94	350	
N.P.	32	10.0	10.1	52.5	54.4	17.1	16.6	47.5	47.5	7.1	6.5	37	43	2.6	2.8	2.5	2.5	93	107	500	
A.H.	23	5.9	7.0	62.2	65.5	17.1	15.9	51.3	56.5	11.2	8.9	31	32	3.5	2.9	3.6	3.9	112	126	400	
Mean ..	29	8.9	9.8	54.9	56.1	17.5	16.9	47.3	48.9	8.5	7.1[1]	43	44	3.6	3.0	2.6	2.7	103	111	413	
Total mean	30	9.9	10.2	54.4	54 3	17.4	16.8[1]	47 4	48.0	7.5	6.6[1]	52	48	3.7	3.1[1]	2 1	2.4[1]	100	110[1]	274	

C.B.F.O_2 = Cerebral blood flow. $CMRO_2$ = Cerebral metabolic rate (oxygen consumption). C.V.R. = Cerebrovascular resistance. M.C.P. = Mean carotid pressure. C.F.P. = Calculated intracranial cerebrospinal fluid pressure.

[1] Denotes a significant change.

down a significant decrease (averaging again 0.6 vol. %) in the arterial oxygen content did exist.

Four patients with brain tumor, all having increased intracranial pressure, were tilted head down 20° from the horizontal. In this group the carotid arterial pressure did not change significantly though a consistent average rise in pressure of 8 per cent (103 to 111 mm. Hg) did occur. There was no real change in cerebral blood flow in this group with this maneuver, and the cerebrovascular resistance did not change significantly though tending to increase in each experiment. The cerebral oxygen consumption decreased an average of 17 per cent in the head-down position but it was not of statistical significance in this group of brain tumor patients considered alone. When considering all experiments (8) using the head-down maneuver, a statistically significant fall in $CMRO_2$ was produced (averaging 17%). In the group of relatively normal individuals the fall in $CMRO_2$ was accounted for by the reduced cerebral blood flow, but in the group of brain tumor patients tilted head down the fall in $CMRO_2$ is the result of the lowering of the arteriovenous oxygen difference, (averaging 1.4 vol. % or 16%). This lowering of the arteriovenous oxygen difference in turn is due to the consistent fall in arterial oxygen content (averaging 0.6 vol. %) and consistent rise in venous oxygen content (averaging 0.9 vol. %). None of the other blood gas analyses showed a change of importance.

There were no important changes in either venous or arterial *p*H in any of the various series of patients studied, neither after tilting the patients head up nor after tilting them head down.

DISCUSSION

In the more normal patients tilting the head up 20° resulted in a fall in mean carotid blood pressure and also a fall in cerebrovascular resistance with the resultant maintenance of the cerebral blood flow. Tilting the normal individual head down 20° increased the mean carotid blood pressure but caused the cerebrovascular resistance to increase even more markedly so that there is a slight but significant decrease (14%) of cerebral blood flow. This latter reduction of cerebral blood flow could possibly be due to increase in contamination of the jugular bulb blood with venous blood of extracerebral origin. In the supine position we have previously shown this to be minimal (5) but with change of position, quite conceivably the contamination could increase and thereby give a lower value for cerebral blood flow and explain as well the drop in cerebral metabolic rate in the head-down position. However, the shape of the nitrous oxide curves obtained from patients in the tilted position did not suggest any increased contamination of the cerebral venous blood obtained from the jugular bulb.

It is therefore probable that the maintenance of the cerebral blood flow at a steady rate despite the altered head of pressure in the carotid vessels,

occasioned by change of position, is accomplished by an appropriate alteration in the cerebrovascular resistance.

In searching for the mechanism of this change in cerebrovascular resistance and in view of the known relationship between altered CO_2 tension and cerebrovascular resistance (6) a most striking finding was the consistent increase in the CO_2 content of the jugular blood in the head-up position and consistent decrease in the head-down position. The apparent validity of this relationship is borne out by the fact that no real change occurred in the jugular CO_2 content in patients with brain tumor tilted either up or down and no related changes in the cerebrovascular resistance occurred in these same patients. However, there was no correlation (r = 0.0) whatsoever between changes in venous CO_2 content and the cerebrovascular resistance.

Another possible explanation for the alteration of cerebrovascular resistance with change of position is the assumption of a nervous control of the cerebral circulation. With this hypothesis the changes of pressure in the carotid vessels serve as the stimuli for alteration of the cerebrovascular resistance. In the head-up position a fall in carotid pressure in normal individuals reflexly causes a relaxation of cerebral vessels (decreased cerebrovascular resistance) and since this is a practiced maneuver in the human, the adjustment is precise. However, the head-down maneuver in normals causes an over-shooting of the mark and the cerebrovascular resistance is increased to the point of actually decreasing the cerebral blood flow. However, only a fair correlation (r = 0.52) was found between the carotid blood pressure and the cerebrovascular resistance in the normal group (fig. 1) and a poorer correlation (r = 0.37) existed between these same factors when the tumor patients were included (fig. 2).

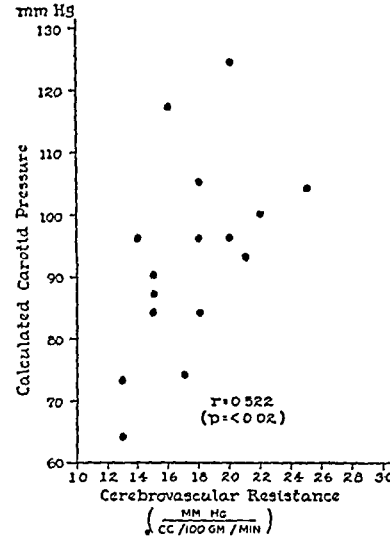

Fig. 1. Relationship between cerebrovascular resistance and calculated carotid pressure in a series of normal individuals before and after a 20° tilt either head up or head down.

Nevertheless, the assumption that the carotid pressure and a neurogenic reflex is normally the controlling factor in altering the CVR may explain the observations in the tumor group of patients. Tumor patients when tilted head up suffered a lesser fall in carotid blood pressure, the cerebrovascular resistance increased and the cerebral blood flow decreased (30%). The failure of the cerebral resistance to decrease may be explained either by the fact that carotid pressure fell to a lesser extent that in normals (6% was

opposed to 17%) and thus was no adequate stimulus for relaxation of vessels or because the reflex controlling this mechanism was depressed by the pathologic process and/or increased intracranial pressure. Tilting the brain tumor patients head down caused an increase in the carotid pressure of 8 per cent and a slight increase in cerebrovascular resistance (5%). The latter change was sufficient to maintain the cerebral blood flow at control values.

The relationship shown in figure 3 reveals the best explanation for the alterations noted in cerebrovascular resistance with change of position. This

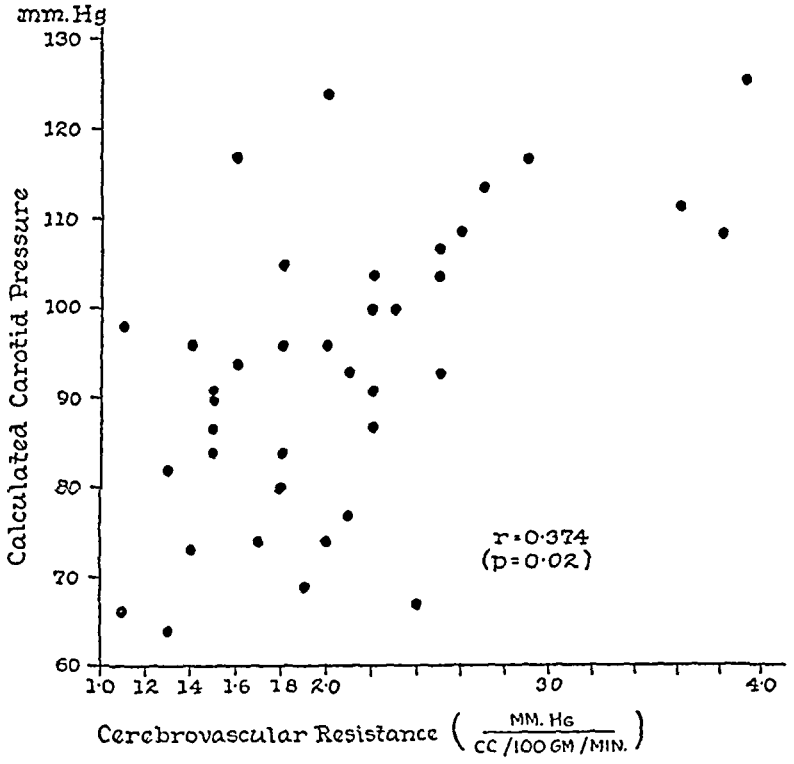

Fig. 2. RELATIONSHIP between cerebrovascular resistance and carotid blood pressure in a series of normal individuals and patients with brain tumor before and after a 20° tilt either head up or head down.

high degree of correlation ($r = 0.72$) would appear to indicate that the change in intracranial cerebrospinal fluid pressure with the change of position is the determining factor in altering the cerebrovascular resistance so as to offset the changes in pressure-head and thus maintain the constancy of the cerebral blood flow. This close relationship of the cerebrovascular resistance with the cerebrospinal fluid pressure has been previously demonstrated (7), the increase in cerebrospinal fluid pressure in patients with brain tumor being associated with a corresponding increase in cerebrovascular resistance. The failure of brain tumor patients to adjust as adequately to change of position as do normal individuals may result from incomplete communication between all parts of the cerebrospinal fluid pathways and the failure of normal changes in in-

tracranial pressure to occur when the patient is tilted. Herniations through the incisura tentorii and/or the foramen magnum in patients with brain tumors, may well partially obstruct the passage of the cerebrospinal fluid at these points. Indeed, measuring the pressure in the lumbar subarachnoid sac in patients with increased intracranial pressure due to brain tumor, tilted head up or down, gave highly inconsistent results, a finding which deviated markedly from similar observation in normal individuals.

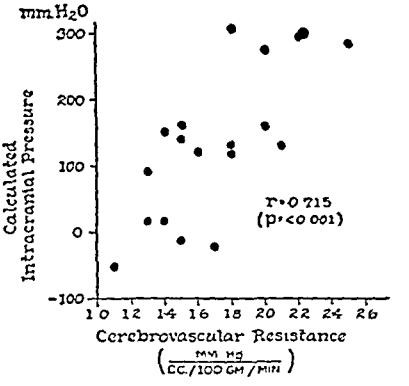

Fig. 3. RELATIONSHIP between cerebrovascular resistance and calculated intracranial pressure in a series of normal individuals before and after a 20° tilt either head up or head down.

With regard to the treatment of brain tumor patients, particularly in the post-operative state, it appears that the head-up position is deleterious, insofar as it distinctly reduces the cerebral blood flow. It has been suggested by some neurosurgeons that a head-up position post-operatively improved drainage from the head and, therefore, is an aid in treatment, particularly of the associated cerebral edema. Occasionally, it appears desirable to lower the head of the unconscious patient, as is frequently the situation with post-operative brain tumor cases, to aid in drainage of the upper respiratory tract or to prevent aspiration of gastric contents or secretions. Our results do not offer any objection to this practice.

SUMMARY

The cerebral circulation and metabolism in unanesthetized humans was studied in the supine position and after tilting either head up or head down 20°. In physiologically normal individuals tilting head up 20° does not change the cerebral blood flow, it being maintained in the face of a fall in carotid blood pressure by a reduction in cerebrovascular resistance. Tilting head down 20° slightly reduced the cerebral blood flow, in spite of an increase in carotid blood pressure. An increase in cerebrovascular resistance in the head-down position explained the lack of increase, and indeed decrease, of the cerebral blood flow in the head-down position.

The possible mechanisms causing the changes in cerebrovascular resistance in the above circumstances are discussed. The best correlation of changes in the cerebrovascular resistance with changes of position was obtained with the calculated changes in intracranial cerebrospinal fluid pressure.

Patients with brain tumors were studied in the supine position and after tilting head up or head down 20°. The mechanisms for adjustment when tilt-

ing these patients head up 20° failed and the cerebral blood flow decreased (30%). Tilting the brain tumor patient head down did not alter the cerebral blood flow. It is, therefore, concluded that the head-up position in the treatment of patients with brain tumor and/or increased intracranial pressure is deleterious; the use of the head-down position in the treatment of such patients does not appear to alter the cerebral blood flow.

We are deeply indebted to Miss Ione Serata for her excellent technical assistance.

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Effects of Folic Acid on Respiratory and Nitrogen Metabolism[1]

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THE USE OF FOLIC ACID in the treatment of certain types of blood dyscrasias has been extensively studied (1–5). Four reviews of the work done in this field have appeared since 1946 (6–9). With the exception of the Jukes and Stokstad review, these are primarily concerned with the hematological effects of folic acid. A search of the literature however reveals that relatively little has been reported concerning the metabolic effects of this substance. Welch (8) in his review pointed out several facts which indicate that folic acid plays an important role in metabolism. Among these are its hematopoietic effect in the macrocytic anemias and its presence in combined form in the majority of animal and human tissues. Other investigators have reported that folic acid functions as an essential substance in the metabolism of bacteria (10), protozoa (11), insects (12), and birds (13–15), as well as in several species of mammals (16–18). These results may be taken as presumptive evidence that this substance plays an equally important role in human metabolism. To obtain direct evidence on this point, experiments were devised to determine the effects of folic acid on the respiratory metabolism, utilization of foodstuffs, and nitrogen balance of both normal human beings and clinical subjects suffering from disorders of the blood-forming organs.

METHOD

Seven normal human beings (5 males, 2 females) and 6 male hospital patients were studied in this investigation. The normal subjects were students attending The Ohio State University and carrying the usual load of curricular and extra-curricular activities. Prior to the beginning of the investigation each normal subject was given a routine hospital physical examination and was reported in good health. The clinical subjects were diagnosed as follows: 3 pernicious anemias, one Hodgkin's disease, one cirrhosis of the liver, and one idiopathic steatorrhea. They had all been hospitalized for at least two weeks previous to their use in this research.

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[1] The work described in this paper was carried out under contract between the Office of Naval Research and The Ohio State University Research Foundation.

All of the subjects, normal as well as clinical, lived in the hospital and were maintained on a weighed diet. Each subject was studied for a period of from 4 to 6 weeks. A 4-day balance period was run each week, extending from breakfast on Tuesday morning to the corresponding time the following Saturday morning. Two or three such balance periods were run on all normal and clinical subjects before the administration of folic acid was begun. In the normal subjects, a few minor adjustments in the diet were usually necessary during the first balance period in order to prevent loss of body weight and to keep the appetite satisfied. After base lines had been established in this way, the administration of folic acid was begun and 30 mg. of this substance was administered intramuscularly daily. Two or three balance periods were then run while folic acid was being given and the results compared with those obtained before the administration of folic acid. Data for nitrogen balance studies were obtained in the following way.

At the beginning of each balance period a stool marker was given and collection of urine was begun. At the end of the 4-day period a second stool marker was given and collection of urine discontinued. Total nitrogen was determined by the Kjeldahl method on all the stools between the two markers and on the urine collected. From these data total nitrogen excretion was calculated. An aliquot portion of the diet was saved each day and analyzed for nitrogen, and the nitrogen intake calculated. From these two figures the nitrogen balance was determined.

Studies on respiratory metabolism, using the Tissot-Haldane technique, were carried out each week according to the following schedule: three times a week, basal determinations, once a week a determination made $1\frac{1}{2}$ hours after a standard meal, and when possible a determination of respiratory metabolism during mild exercise. This exercise test consisted of a preliminary 5-minute rest period in the sitting position, a 5-minute period of walking on a horizontal treadmill at the rate of 35 meters per minute, followed by a 5-minute recovery period in the sitting position. Expired air was collected continuously during the walking and recovery periods. In spite of the mild form of this exercise, only two clinical subjects were able to take the test.

Before each of the basal and postprandial tests the subject emptied the bladder, noting the time. At the end of the determination the bladder was again emptied and the elapsed time recorded. From these samples the total urinary nitrogen for each respiratory metabolism test period was determined by the Kjeldahl method. From the experimental results the following data were calculated: expiratory volume, O_2 consumption, CO_2 production, protein metabolism, non-protein *R. Q.*, and the percentage of total calories derived from each of the organic nutrients.

Studies on peripheral blood including red cell, reticulocyte, and differential counts were conducted five times a week. Bone marrow biopsies were done

once a week and differential cell counts and *in vitro* cellular oxygen consumption determinations were carried out in a standard Fenn apparatus.

Two additional clinical subjects were studied similarly, except that the injection of liver extract was substituted for folic acid therapy, and one of the six subjects that received folic acid treatment was given liver extract for two weeks following a 3-week period of folic acid therapy. This made possible a comparison of the metabolic effects of these two anti-anemic substances.

RESULTS

In tables 1 and 2 descriptive data on each of the normal and clinical subjects are given. The experimental results obtained are listed in tables 3, 4, 5 and 6. Each value given in the tables is the numerical average of all tests run before or during folic acid and liver extract administration. With the exception of peripheral blood studies, all data have been subjected to statistical

TABLE 1. DESCRIPTIVE DATA ON NORMAL SUBJECTS RECEIVING 30 MG. OF FOLIC ACID INTRAMUSCULARLY DAILY

SUBJECT	AGE	SEX	COLOR	HEIGHT	WEIGHT	OCCUPATION
				inches	*lbs.*	
A.E.	24	M	W	72.6	187	Medical Student
H.F.	20	F	W	65.0	156	Physical Education Student
R.H.	22	F	W	68.8	142	Home Economics Student
S.J.	23	M	W	68.8	133	Medical Student
L.P.	19	M	B	68.1	128	Pre-Medical Student
J.V.	23	M	W	68.6	119	Student in Languages
D.Y.	20	M	B	69.1	148	Student in College of Arts

analysis. The *t* test was used and all changes which were significant to the 5 per cent level have been indicated in the tables.

In column 2 of tables 3 and 4, the average reticulocyte count is shown for both normal and clinical subjects. With the normal subjects there was no significant change in the peripheral reticulocyte level during folic acid administration. However, 4 of 6 clinical subjects showed increases in the reticulocyte response averaging about 6.5 per cent. As might be expected, the greatest increases were obtained in the clinical subjects suffering from pernicious anemia (*Y. O.*, *M. O.* and *M. F.*). There was a similar but less marked response in the two clinical subjects receiving liver extract as shown in the same table. The peripheral red blood cell counts listed in column 3, tables 3 and 4, show no significant change in normal subjects during folic acid administration. With the clinical subjects, however, there was an increase in peripheral red blood cells during folic acid administration in 3 subjects (*Y. O.*, *M. O.* and *M. F.*). These are the same subjects who showed the greatest reticulocyte response.

Results on cellular bone marrow studies corroborate the results reported

TABLE 2. DESCRIPTIVE DATA ON CLINICAL SUBJECTS RECEIVING 30 MG. OF FOLIC ACID INTRAMUSCULARLY DAILY

SUBJECT	AGE	SEX	COLOR	HEIGHT	WEIGHT	MARITAL STATUS	OCCUPATION	SYMPTOMS	DIAGNOSIS	RESULT OF TREATMENT
				inches	*lbs.*					
H.D.	38	M	W	69.1	110	Single	Unemployed	Loss of sense of touch, stiffness, generalized weakness, diarrhea, loss of weight	Idiopathic steatorrhea	Improved
A.M.	39	M	W	77.7	151	Divorced	Unemployed	Swelling of abdomen and ankles, ulcer on foot, fever, chills	Cirrhosis of the liver	Improved
V.M.	63	M	W	74.2	121	Married	Unemployed	Weakness, loss of weight, swollen lymph nodes	Hodgkin's disease	Unimproved
M.O.	60	M	W	66.6	128	Single	Dishwasher	Loss of weight, weakness, pallor, languor	Addisonian pernicious anemia	Improved
Y.O.	65	M	W	70.6	161	Married	Farmer	Sallow color, weakness, loss of weight, languor	Addisonian pernicious anemia	Improved
M.F.	48	M	W	65.0	115	Married	Laborer	Increasing weakness, intermittent sore tongue, shortness of breath, weight loss, and loss of appetite	Addisonian pernicious anemia	Improved

by previous investigators (Spies, Moore, Doan *et al.*) and need not be discussed in this paper. The bone marrow cellular respiration on whole bone marrow suggested a rise in respiration values during folic acid therapy and this could be correlated with an increase in reticulocyte count. However, difficulty in obtaining bone marrow biopsies without dilution with peripheral blood makes these data inconslusive. They are therefore neither tabulated nor discussed.

Basal values for the O_2 consumption, CO_2 production, nitrogen excretion, non-protein *R. Q.'s* and percentage basal calories derived from each of the organic nutrients are given in tables 3 and 4. There was no significant change

TABLE 3. AVERAGE BASAL RESPIRATORY METABOLISM IN NORMAL SUBJECTS BEFORE AND DURING FOLIC ACID ADMINISTRATION

SUBJECT	1 NO. BLOOD DETERMINATIONS	2 RETICULOCYTES	3 R.B.C.	4 NO. B.M.R. TESTS	5 BASAL OXYGEN CONSUMPTION	6 BASAL CO_2 PRODUCTION	7 BASAL N_2 EXCRETION	8 BASAL NON PROTEIN *R.Q.*	9 PERCENTAGE TOTAL BASAL CALORIES FROM		
									PROTEIN	CHO	FAT
		%	*millions*		*cc/min.*	*cc/min.*	*gm/hr.*				
S.J. Before	9	2.6	4.7	6	207	174	.38	.85	17	40	43
During	10	2.6	5.4	6	210	187	.52	.92[1]	23	56[1]	21
J.V. Before	10	1.3	5.6	6	217	177	.46	.82	20	31	49
During	11	1.1	6.2	6	212	179	.45	.84[1]	20	40[1]	40
L.P. Before	12	1.7	5.1	7	212	184	.51	.89	22	49	29
During	11	1.5	5.2	5	204	178	.51	.89	22	49	29
D.Y. Before	12	1.5	5.0	7	219	178	.49	.82	21	30	49
During	11	1.6	5.0	5	211[1]	178	.55	.85[1]	24	38[1]	38
A.E. Before	10	1.2	5.3	7	261	208	.60	.79	22	23	55
During	9	1.4	5.3	5	254	210	.50	.83	19	35	46
R.H. Before	11	0.8	4.6	10	193	162	.67	.84	31	33	36
During	16	1.2	4.5	8	198	166	.67	.86	32	34	34
H.F. Before	14	1.7	4.7	10	205	176	.54	.88	24	43	33
During	16	1.6	4.8	8	205	172	.52	.85	24	38	38

[1] Statistically significant change to 5% level.

in the basal oxygen consumption of the normal subjects during the administration of folic acid (column 5). On the other hand, all six of the clinical subjects listed in part *A* of table 5 showed a drop in the basal oxygen consumption during the administration of folic acid. In *subjects A. M.* and *V. M.* this drop was too slight to be significant. In *subject M. F.* the decrease amounted to 5 per cent but the variability of the data is so great that this figure is not statistically significant. The three remaining subjects, *M. O.*, *H. D.*, and *Y. O.*, all showed statistically significant drops in basal oxygen consumption. It is interesting to note that the magnitude of this drop in oxygen consumption parallels in a general way the changes in the peripheral blood picture. The clinical subjects that showed the most marked improvement in the blood picture also showed a significant drop in oxygen consumption.

In figure 1 the peripheral red blood cell count and basal oxygen consumption in a typical normal subject (*L. P.*) have been plotted. It can be seen from this graph that there was no effect of folic acid administration on either red cell count or basal oxygen consumption. In figure 2 a similar graph on a clinical subject (*Y. O.*) suffering from pernicious anemia is presented. In his case, administration of folic acid was followed by an increase in the red cell count and a decrease in the basal oxygen consumption.

TABLE 4. AVERAGE BASAL RESPIRATORY METABOLISM IN CLINICAL SUBJECTS BEFORE AND DURING FOLIC ACID ADMINISTRATION

SUBJECT		*1* NO. BLOOD DETERMINATIONS	*2* RETICULOCYTES	*3* R.B.C.	*4* NO. B.M.R. TESTS	*5* BASAL OXYGEN CONSUMPTION	*6* BASAL CO_2 PRODUCTION	*7* BASAL N_2 EXCRETION	*8* BASAL NON PROTEIN *R.Q.*	*9* PERCENTAGE TOTAL BASAL CALORIES FROM	*10*	*11*
										PROTEIN	CHO	FAT
			%	*millions*		*cc/min.*	*cc/min.*	*gm/hr.*				
A. Clinical Subjects Receiving Folic Acid												
A.M.	Before	11	1.7	4.1	6	270	216	.31	.80	11	28	61
	During	9	2.0	3.9	5	267	213	.24	.80	8	29	63
V.M.	Before	8	1.6	4.3	7	227	187	.29	.83	12	37	51
	During	9	1.8	4.2	5	226	186	.27	.82	11	36	53
Y.O.	Before	11	3.1	1.7	7	273	205	.28	.75	9	14	77
	During	11	13.6	2.2	5	234[1]	189	.24	.81[1]	10	33[1]	57
M.O.	Before	10	8.0	1.7	7	210	171	.23	.82	10	35	45
	During	15	12.2	2.3	5	199[1]	176	.23	.90[1]	10	58[1]	32
M.F.	Before	10	1.1	1.5	2	219	170	.22	.78	10	21	69
	During	22	18.8	2.0	7	207	162	.32	.77	14	20	66
H.D.	Before	10	1.6	4.3	6	197	145	.28	.72	13	7	80
	During	18	1.8	4.4	8	183[1]	140	.27	.76[1]	14	13[1]	73
B. Clinical Subjects Receiving Liver Extract												
H.D.[2]	During	5	1.5	4.2	5	202	168	.31	.83	15	35	50
C.A.	Before	7	4.4	2.4	6	177	138	.43	.77	23	17	60
	During	23	7.1	2.6	9	167	136	.28	.81[1]	16	31[1]	53
R.S.	Before	8	2.6	1.5	3	242	187	.22	.77	9	20	71
	During	20	10.3	2.9	9	202[1]	175	.19	.87[1]	9	50[1]	41

[1] Statistically significant to 5% level.

[2] *Subject H. D.* received liver extract for a 2-week period immediately after a 3-week period on folic acid.

The basal oxygen consumption of two of the three patients receiving liver extract as shown in part *B* of table 4 also decreased markedly coincident with the beginning of therapy. In the case of *subject R. S.* this decrease is statistically significant, but with *subject C. A.*, the significance is questionable. The third patient in this group, *H. D.*, was given liver extract following three weeks of treatment with folic acid, and the change to liver therapy was accompanied by a slight increase in oxygen consumption which is not significant.

TABLE 5. AVERAGE SPECIFIC DYNAMIC ACTION IN NORMAL AND CLINICAL SUBJECTS BEFORE AND DURING FOLIC ACID ADMINISTRATION

SUBJECT		1 NO. OF TESTS	2 BASAL OXYGEN CONSUMPTION	3 RESTING O_2 CONSUMPTION 1½ HOURS AFTER FOOD	4 PERCENTAGE INCREASE AFTER FOOD
			cc/min.	*cc/min.*	
A. Normal Subjects Receiving Folic Acid					
S.J.	Before	2	209	298	43
	During	2	205	315	54
J.V.	Before	2	209	273	31
	During	2	219	289	32
L.P.	Before	2	228	281	23
	During	2	204	282	38
D.Y.	Before	2	219	300	37
	During	2	212	301	42
A.E.	Before	2	259	330	27
	During	2	256	317	24
R.H.	Before	3	197	232	18
	During	3	200	269	35
H.F.	Before	3	215	273	27
	During	3	208	257	23
B. Clinical Subjects Receiving Folic Acid					
A.M.	Before	2	267	300	13
	During	2	272	326	20[1]
V.M.	Before	2	227	265	17
	During	2	230	289	25[1]
Y.O.	Before	2	278	308	11
	During	2	232	279	21[1]
M.O.	Before	2	216	269	24
	During	2	194	263	36[1]
M.F.	Before				
	During	1	209	213	5
H.D.	Before	2	199	213	7
	During	3	182	207	14[1]
C. Clinical Subjects Receiving Liver Extract					
H.D.[2]	During	2	185	238	29
C.A.	Before	2	179	240	34
	During	3	172	231	34
R.S.	Before	1	234	254	8
	During	3	195	241	27[1]

[1] Statistically significant change to 5% level.

[2] *Subject H. D.* received liver extract for a 2-week period immediately after a 3-week period on folic acid.

As might be expected, the findings on CO_2 production parallel the results obtained on O_2 consumption. The administration of folic acid produced no significant change in the CO_2 production of normal subjects, but in all but one of

the clinical subjects it was followed by a decreased CO_2 production. This decrease averaged 4 per cent. The basal nitrogen excretion, which is shown in column 7 of tables 3 and 4, was not significantly changed in either normal or clinical subjects. Even the increase in excretion in *subject S. J.* is not significant as this subject showed a high degree of variability. With the clinical subjects, all but two (*M. O.* and *M. F.*) showed drops in basal nitrogen excretion, which are not statistically significant.

The basal non-protein respiratory quotients calculated from the data tabulated in columns 5, 6, and 7 are shown in column 8 of tables 3 and 4. In all but two of the normal subjects the *R. Q.* rose during the administration of

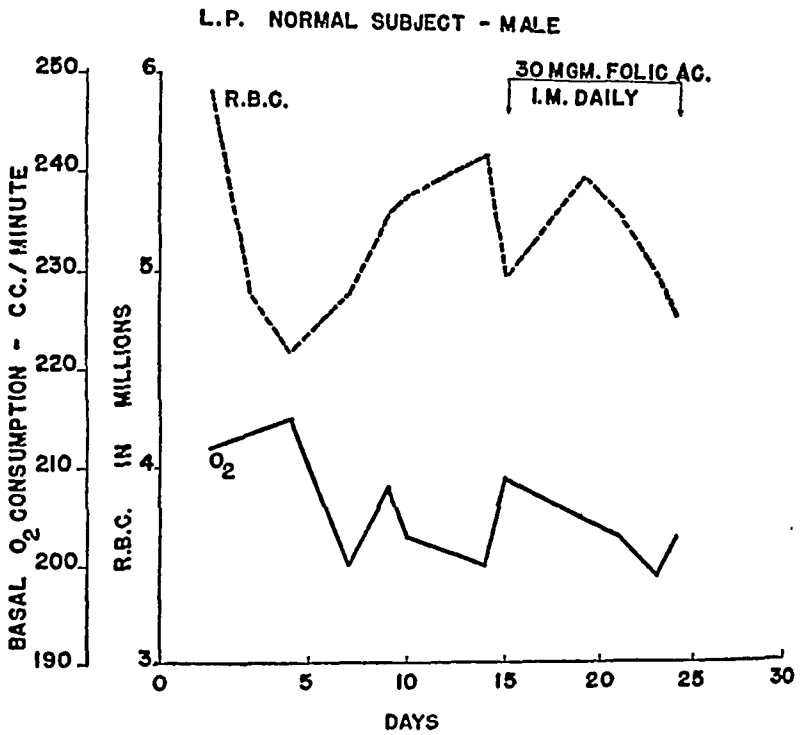

Fig. 1. TYPICAL CURVES showing changes in erythrocyte count and in basal oxygen consumption of normal subject before and during administration of folic acid.

folic acid. These rises were statistically significant in 3 subjects, *S. J.*, *J. V.*, and *D. Y.* Among the clinical subjects the *R. Q.* showed a statistically significant rise during folic acid administration in 3 cases, *H. D.*, *Y. O.*, and *M. O.*, and during liver therapy in 2 cases, *C. A.* and *R. S.* In the others there was no significant change.

In neither the clinical nor the normal subjects was there a significant change in the percentage of total basal calories obtained from protein (column 9). However, 5 of the 7 normal controls showed a marked increase in the percentage of calories derived from carbohydrates (column 10), while 3 of the clinical subjects (*H. D.*, *Y. O.*, and *M. O.*) receiving folic acid and 2 receiving liver extract showed a similar effect. The changes in percentage of total calories

derived from fat as shown in column 11 are of course the reverse of those reported for carbohydrates. Since these figures are calculated from the non-protein *R. Q.*, the changes are significant only in those individuals in which there was a significant rise in the *R. Q.*

As can be seen in table 5, 5 of the 7 normal subjects showed an increase in specific dynamic action during the administration of folic acid, while 5 clinical subjects receiving folic acid (no satisfactory tests were run on the sixth) and

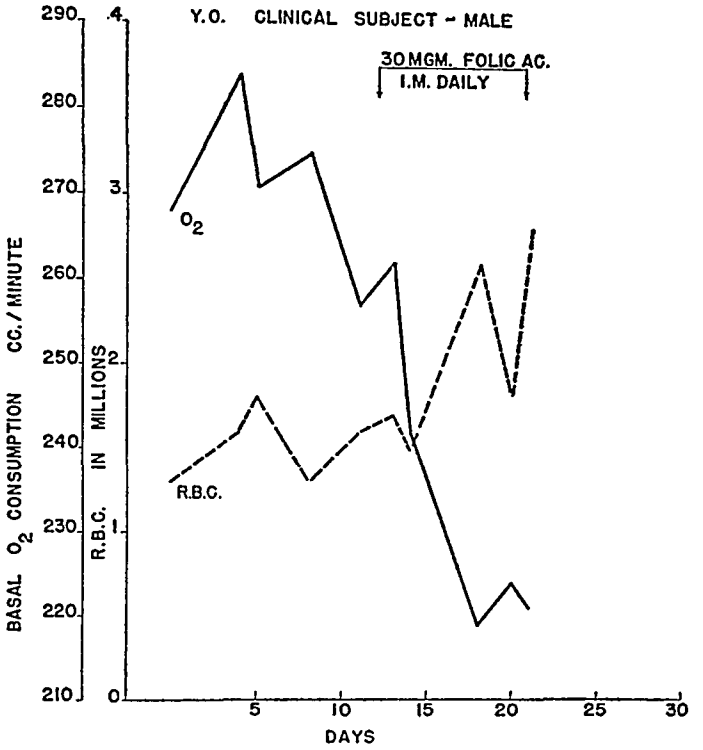

Fig. 2. TYPICAL CURVES showing changes in erythrocyte count and in basal oxygen consumption of clinical subject before and during administration of folic acid.

one receiving liver extract showed a similar increase. The changes are statistically significant with the clinical, but not with the normal subjects.

The results obtained in the exercise experiments showed a high degree of variability, and there was no indication of any consistent effect of folic acid administration. Therefore, these results have not been tabulated or discussed.

The average daily food intake for the normal and clinical subjects before and during the administration of folic acid is listed in column 1 of table 6. These figures are based on calculations from the tables of Bowes and Church (19). It can be seen that for all practical purposes the food intake of the normal subjects remained constant throughout the period of study. There were a few

minor variations in the caloric intake before folic acid administration which were made in the first week and were necessary to prevent loss of body weight and to keep the appetite of the subjects satisfied. In the case of the clinical subjects, however, the figures show conclusively that in every case there was an increased caloric intake during folic acid administration which averaged 25 per cent. This was due to an increased consumption of all three nutrients, although the greatest increase occurred in carbohydrate consumption.

The nitrogen intake of normal and clinical subjects, listed in column 2 of table 6, shows that with the normal subjects there was a slight daily decrease (0.2 gm., 1.1%) during the administration of folic acid. This difference is not significant and the nitrogen intake may therefore be considered constant throughout the experiment. In the case of the clinical subjects, the daily nitrogen intake showed an increase during folic acid administration in all but *Y. O.* This increase averaged 1.4 gm. or about 12 per cent and was statistically significant. Nitrogen balance studies on clinical *subject M. F.* could not be carried out because of a complicating pneumonia which developed in the course of the experiment.

Column 5, table 6, lists the average daily nitrogen excretion for the normal subjects. Before folic acid administration this averaged 13.7 gm. During folic acid administration the total nitrogen excretion averaged 14.3 gm. This represents an increase in total nitrogen excretion during folic acid administration of 0.6 gm. (4.4%) which is not statistically significant. The average daily urinary nitrogen excretion increased following the administration of folic acid, 0.5 gm. (about 4%). However, only 4 of the 7 subjects showed an increase and statistically there was no significant change in the output of urinary nitrogen. The average daily fecal nitrogen increased during folic acid administration in 6 of the 7 subjects. This increase averaged 0.22 gm. daily (18%), and is statistically significant. Therefore, the increased fecal nitrogen which occurred during folic acid administration in the normal subjects was the only significant change in the nitrogen output of this group.

The average daily total nitrogen excretion for the clinical subjects is listed in column 5 of the same table. Before folic acid administration this average was 9.8 gm. while during folic acid administration the average value was 8.6 gm., a decrease of 1.2 gm. or about 12 per cent.

The average daily urinary nitrogen output decreased from 7.6 gm. before to 7.2 gm. during the administration of folic acid. This is a 6 per cent decrease. The fecal nitrogen similarly decreased from an average daily value of 2.0 gm. before to 1.4 gm. during folic acid administration, a decrease of more than 30 per cent.

In column 6 the daily nitrogen balances for the normal and clinical subjects are given. It will be noted that all the normal subjects were in a positive nitrogen balance and remained so throughout the experiments. The average daily

retention before folic acid administration was 4.1 gm. per day. During the administration of folic acid, the nitrogen balance averaged +3.3 gm. This is an average decrease during folic acid administration of 0.8 gm. (almost 20%). Similarly, the results on the nitrogen balances of the clinical subjects showed that all were in a positive nitrogen balance, and remained so throughout the experiment. The nitrogen retention before folic acid administration averaged +1.80 gm. per day. During the administration of folic acid, the nitrogen balances averaged +4.20 gm., an increase of 140 per cent, which is statistically significant.

The body weights for both normal and clinical subjects before and during folic acid administration are shown in column 7, table 6. It can be seen that the body weights remained practically constant for both normal and clinical subjects throughout the period of study.

Nitrogen balance studies on one female and one male clinical subject, both of whom exhibited a macrocytic anemia, were also carried out before and during a course of liver extract therapy. The nutritional responses to the liver extract were similar in some respects to the results obtained with folic acid. However, the results are inconclusive because of the limited number of subjects investigated. These results have therefore not been included in table 6.

CONCLUSIONS AND DISCUSSION

The results obtained in this investigation, and reported in detail in the preceding section, indicate that the administration of folic acid produced at least 5 definite metabolic effects:

1) Clinical subjects undergoing folic acid treatment showed a marked increase in appetite which was accompanied by a definite euphoria. The effect on carbohydrate intake was most marked, although there was also an increase in the consumption of protein and of fat. Euphoria occurred usually within 24 hours after the beginning of the administration of folic acid. This effect was most marked in cases of macrocytic anemia. These clinical subjects, as was to be expected, were the ones in which the greatest hematological response to folic acid occurred. These findings are in agreement with the results reported by Doan, Wilson and Wright (20); Darby *et al.* (21); Spies (22); Spies *et al.* (23); and Goldsmith (24). No such effect was noted in any of the normal controls.

2) In these experiments the basal oxygen consumption of *subjects Y. O., M. O.* and *M. F.*, who were suffering from pernicious anemia was definitely reduced following the administration of folic acid. These were the subjects that showed the most pronounced hematological response to folic acid therapy. It has been reported by several investigators (25–27) that there is an elevation of basal metabolism in patients suffering from anemias. These reports indicate that the most pronounced elevation of metabolism occurs in pernicious anemia. It has been postulated by Richards and Strauss (28), Alt (29) and Baldridge

and Barer (30) that the increased metabolism is due to the additional respiratory and circulatory effort required in furnishing the tissues of an anemic patient with an adequate supply of oxygen. The results reported in this paper are in harmony with this theory. Following the reticulocyte responses, which of

TABLE 6. AVERAGE DAILY FOOD INTAKE AND NITROGEN BALANCE IN NORMAL AND CLINICAL SUBJECTS BEFORE AND DURING FOLIC ACID ADMINISTRATION

SUBJECT	1	2	3	4	5	6	7
	FOOD INTAKE		NITROGEN OUTPUT			NITROGEN BALANCE	BODY WEIGHT
			Urine	Feces	Total		
	cal/day	N gm/day	gm/day			gm/day	lb.
A. Normal Subjects							
S.J. Before	3310	21.2	7.6	1.6	9.2	+12.0	134
During	3400	21.0	11.0	0.9	11.9	+9.1	136
J.V. Before	2330	17.9	11.9	0.8	12.7	+5.2	120
During	2510	18.5	12.6	1.2	13.8	+4.7	120
A.E. Before	2170	17.2	14.6	1.2	15.8	+1.4	184
During	2190	16.6	13.8	1.8	15.6	+1.0	178
D.Y. Before	2710	18.7	14.8	1.3	16.1	+2.6	145
During	2850	17.8	14.0	1.7	15.7	+2.1	145
L.P. Before	2710	18.7	13.4	1.5	14.9	+3.8	129
During	2850	17.8	13.3	1.9	15.2	+2.6	130
R.H. Before	2230	15.3	13.0	1.2	14.2	+1.2	142
During	2450	15.9	13.1	1.5	14.6	+1.3	142
H.F. Before	2230	15.3	11.8	1.1	12.9	+2.4	154
During	2420	15.8	12.4	1.2	13.6	+2.2	151
B. Clinical Subjects							
H.D. Before	1530	9.9	4.7	5.0	9.7	+0.2	111
During	1980	13.2	6.1	3.5	9.6	+3.6	107
V.M. Before	1870	13.0	11.0	1.6	12.6	+0.4	121
During	2150	14.4	11.2	0.9	12.1	+2.3	120
A.M. Before	2340	14.5	8.5	1.3	9.8	+4.7	153
During	2730	15.2	6.9	0.8	7.7	+7.5	154
Y.O. Before	1780	9.1	7.1	1.0	8.1	+1.0	159
During	2120	8.3	5.7	1.0	6.7	+1.6	158
M.O. Before	2230	10.6	6.8	1.3	8.1	+2.5	124
During	2960	13.0	5.9	0.9	6.8	+6.2	125

course resulted in a marked increase in the number of red blood cells available, the basal oxygen requirement of the clinical subjects was definitely reduced, and it may be assumed that this reduced oxygen utilization was the result of a decreased demand upon the respiratory and circulatory mechanisms for the maintenance of an adequate oxygen supply to the tissues. Since the blood picture of the normal controls was not significantly affected by the administration of folic acid, no effect on basal oxygen consumption of these subjects was to be expected.

3) The clinical subjects suffering from macrocytic anemias and 5 of the normal controls showed an increased utilization of carbohydrate during the administration of folic acid. Among the clinical subjects this effect was most pronounced with those who showed the most significant decrease in basal oxygen and who, it should be remembered, were also the ones showing the most pronounced hematological response. It should be kept in mind that the validity of this conclusion rests upon the assumption that the non-protein *R. Q.'s* are true metabolic quotients and were not influenced by changes in ventilation volume, acid-base balance, or other fortuitous conditions. Since the determinations of oxygen consumption and CO_2 output were all made under identical conditions, and since the normal and clinical subjects were all on a controlled diet, there is no reason to doubt the validity of these respiratory quotients, and hence it is believed that this increase in carbohydrate utilization is a true metabolic effect of folic acid. We have no explanation to offer for this effect. It might seem logical to assume that since the food intake of the clinical subjects increased during folic acid administration, the consequent increased carbohydrate intake was the cause of increased utilization of this substance. However, a statistical treatment of these data indicated that there was in these experiments, no significant relationship between carbohydrate intake and the percentage of total calories derived from carbohydrates. Before a satisfactory explanation can be offered for these results, further studies must be made. These studies should include blood sugar determinations and, perhaps even more important, an investigation of the effects of folic acid on the various enzyme systems concerned in carbohydrate metabolism.

4) In all of our clinical subjects and in about one half of the normal controls, there was an increased specific dynamic action during the administration of folic acid. It is possible that this effect is the result of a beneficial action of folic acid on the absorption of foodstuffs from the intestinal tract. It is impossible at the present time to suggest the mechanisms by which such an effect might be produced.

5) The data on nitrogen metabolism indicate that the administration of folic acid had significant effects on nitrogen balance. The fact that the average nitrogen retention of the normal subjects decreased 20 per cent after the administration of folic acid, while the urinary nitrogen increased 4 per cent and the fecal nitrogen 18 per cent, suggests that folic acid may interfere with the absorption of nitrogen-containing substances by the mucosa of the gastrointestinal tract and may also increase the deaminization of amino acids by the liver. Further experimentation is necessary before the mechanism by which these effects are produced can be elucidated.

In the case of clinical subjects, the administration of folic acid produced exactly those effects which might have been expected. First, there was a marked

increase in appetite as noted in no. 1. Second, the administration of folic acid was followed by a significant increase in nitrogen retention. Four of the 5 clinical subjects showed a marked and significant decrease in fecal nitrogen, while with 3 of the 5 subjects the urinary nitrogen decreased significantly. This would indicate that the effect on nitrogen retention was of two sorts and exactly opposite to that observed in normal subjects: first, an increased absorption of amino acids and other nitrogen-containing compounds from the gastrointestinal tract; and second, decreased deaminization of absorbed amino acids by the liver, which was probably due to the fact that an increased percentage of these amino acids was utilized in the synthesis of hemoglobin and tissue proteins. These findings are in agreement with the results reported by Heath and Taylor (31), who showed that the regeneration of blood cells which occurs during remissions in anemia is accompanied by increased nitrogen retention.

While our investigations of the metabolic responses to liver extract were limited, and therefore inconclusive, it is nevertheless true that the results reported in this paper indicate that liver extract produces metabolic effects similar to those observed following folic acid administration. This might very well be expected on the assumption that these two anti-anemic substances act in a similar way to produce their effects. Furthermore, in the single clinical subject diagnosed as idiopathic steatorrhea, in which liver extract was administered following folic acid therapy, it appears that this sequence of therapy produced the more beneficial response. It should be pointed out that Meyer (32) suggests that liver extract injections supplemented by small doses of folic acid produce more beneficial effects both neurologically and hematologically than does either substance alone.

SUMMARY

The metabolic effects of folic acid administration have been investigated on 7 normal and 6 clinical subjects (3 pernicious anemias, one Hodgkin's disease, one cirrhosis of the liver, and one idiopathic steatorrhea). The results indicate that the administration of folic acid produced the following effects: 1) Euphoria, increased appetite, and increased caloric intake in all 6 clinical subjects; 2) decreased basal oxygen consumption in the clinical subjects, particularly those suffering from pernicious anemia, but no change in the basal oxygen consumption of normal subjects; 3) an increase in the percentage of total calories derived from carbohydrate in both normal and clinical subjects; 4) an increase in specific dynamic action in all clinical subjects and in 4 of 7 normal controls; 5) an increase in fecal nitrogen and a decrease in nitrogen retention in normal subjects and an increase in nitrogen retention of all clinical subjects. The latter effect was the result of three factors: first, an increased protein intake; second, a decreased fecal nitrogen; and third, a decreased uri-

nary nitrogen in 3 of 5 cases (2 pernicious anemias and one cirrhosis of the liver). These results suggest that in the clinical subjects folic acid increased the absorption of nitrogen from the gastrointestinal tract and decreased the deamination of amino acids by the liver. This latter effect is probably associated with increased utilization of nitrogen-containing compounds in the synthesis of hemoglobin and tissue proteins.

The authors wish to express their indebtedness to the Lederle Laboratories for their generosity in furnishing the folic acid, to the Statistics Laboratory of The Ohio State University, particularly Professor Donald R. Whitney, who carried out the statistical analysis of our data, to Mrs. Martha Lewis, Director of the Dietary Department, who gave valuable assistance in organizing the dietary regime, to Dr. Clifford Angerer, who carried out the *in vitro* studies on bone marrow oxygen consumption, to Mr. Laurel Prince, Mrs. Phyllis Arscott O'Neill and Mrs. June Monnen Swanson, all of whom gave technical assistance, and finally to the various persons who served as subjects and without whose complete cooperation this investigation would have been impossible.

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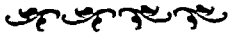

Arginase Activity of Blood in Normal Children and Pregnant Women

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In connection with a long-range study of the relationship of blood enzymes to the growth and development of children an analysis of the arginase activity of the erythrocytes was undertaken. Data obtained from 120 healthy children, 18 pregnant women, 11 adult females and 12 adult males are reported.

METHODS

Blood was collected by finger puncture from the children and vein puncture from the adults. No difference in arginase activity was found between capillary and venous blood. Sodium heparinate[1] was used as the anticoagulant since it did not affect the enzyme activity.

Arginase activity was measured using the substrate of Hunter and Downs (1) and adapting the procedure of Kochakian (2) to a micro scale. Fifty cu. mm. of blood were transferred to 5.9 ml. of 0.00017 per cent cobaltous chloride, and the tube was heated in a water bath at 45° to 50°C. for 20 minutes in order to activate the enzyme. Following this, 2 ml. of the Hunter and Downs' buffered substrate were added and the tube incubated at 37.0°C. ± .05°C. for 6 hours. The enzymatic activity was stopped by adjusting the tube to *p*H 6.0 and heating for 5 minutes in a boiling water bath. After incubation of the urea with crystalline urease (3), the ammonia was determined by micro-Kjeldahl using the mixed indicator of Ma (4). All samples were analyzed in duplicate in batches of 10 to 20 samples. Erythrocyte counts were made following the procedure of Blum (5) after calibration of the Evelyn colorimeter.

A 6-hour period of incubation was chosen as the length of time necessary to give a sufficient quantity of urea for determination and yet not too long a period to cause any loss of enzyme activity. Since it was found that the enzyme activity is directly proportional to the urea formed, calibration curves are unnecessary. We have defined an arginase unit as that amount of cobalt activated enzyme which, under the conditions described, will form 0.25 mg. of urea nitrogen in 6 hours. Our unit is equivalent to about 1/12 Hunter and Downs' unit.

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[1] The authors are indebted to J. A. Aeschlimann, Hoffmann-La Roche Inc., Nutley, New Jersey, for a generous supply of the purified sodium salt of heparin.

Analysis of the data obtained from 25 consecutive determinations indicates that the average deviation of duplicates from their mean is ±2.0 per cent with a range of 0 to 4.8 per cent.

RESULTS

Figure 1 shows the wide variation in the arginase activity of blood obtained from children. Table 1 shows that there is no significant change in enzyme activity with age, but that there is a definite sex difference with males having, on the average, 86 per cent of the blood arginase activity of females. This sex difference is highly significant ($P < .0001$) as shown by t analysis (6) of the data given in table 1. Eighty-one of the 120 children first tested were reassayed one year later with the striking result shown in figure 2. Variance analysis (7) of these data gave a product-moment correlation of 0.83, showing

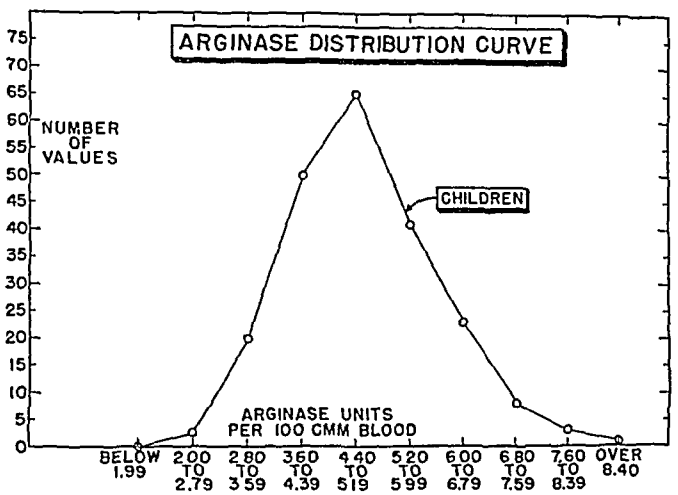

Fig. 1

that the relative position of the individual in the group is subject to but little variation.

The mean arginase activity of 12 normal males, ranging in age from 29 to 57 years, was 0.98 units per rbc × 10^8 with a range of 0.41 to 1.23. The mean value for adult males checks with the value (0.96 units/rbc × 10^8) obtained from male children.

The data obtained using pregnancy cases are presented in table 2. It can be seen that there is no change which can be regarded as significant. The slight drop found in whole blood arginase activity during pregnancy is explained by the drop in red cell count. The sex difference in adults, obtained by comparing the red cell concentration of arginase in the pregnancy cases (N = 72) with the adult males (N = 12), borders on significance ($P = 0.08$).

Table 3 shows the constancy of whole blood arginase from day to day and reveals that the small changes found are probably due to variation in red cell count and experimental error.

DISCUSSION

A marked sex difference has been reported in the arginase activity of the liver (8, 9) and blood (10) of mature rats. Covolo and West (11) reported that

TABLE 1. ARGINASE ACTIVITY OF BLOOD OF CHILDREN

SUBJECTS			ARGINASE			
AGE RANGE	SEX	N	MEAN	SIGMA[1]	MEAN	SIGMA[1]
months			*Units/100 cu mm. blood*		*Units/rbc* × 10^3	
72–95	M	19	4.39	0.64	0.97	0.13
	F	18	5.24	1.50	1.19	0.32
Total		37	4.80	1.22	1.08	0.27
96–119	M	14	4.69	0.79	1.00	0.17
	F	16	5.27	1.63	1.13	0.33
Total		30	5.00	1.34	1.07	0.27
120–143	M	12	4.71	1.27	0.99	0.30
	F	21	4 96	0.80	1.10	0.17
Total		33	4.87	1.00	1.06	0.23
144–167	M	19	4.54	0.74	0.98	0.16
	F	25	5.25	0.88	1.18	0.25
Total		44	4.94	0.89	1.09	0.24
168–191	M	17	4.85	1.21	1.01	0.23
	F	19	5.27	0.98	1.09	0.21
Total		36	5.07	1.11	1.05	0.22
192–215	M	14	4.24	0.96	0.84	0.17
	F	11	5 83	0.85	1.17	0.16
Total		25	4.94	1.21	0.99	0.23
Total	M	98	4.56	0.94	0.96	0.20
	F	110	5.26	1.16	1.14	0.25
Total		208	4.93	1.12	1.06	0.25

[1] $\sigma = \sqrt{(1/N)(\Sigma X^2) - M_X^2}$

blood from adult male individuals showed about 79 per cent[2] of the arginase activity of female blood while calculations from the data of Takehara (12) reveal male blood to have, on the average, about 90 per cent of the activity of blood obtained from females. Our data reveal that this sex difference, unlike that found in the rat, is present before pubescence and, therefore can hardly be the result of gonadal hormone action.

[2] There is an error in their table of normal values. For 7 normal men, a mean value of 8.9 is given, although the mean of the cases actually tabulated is 7.4. The mean of 11.2 given for 9 normal women agrees with the mean of the cases tabulated.

Histamine as Possible Chemical Mediator for Cutaneous Pain: Painful Responses on Intradermal Injection of Perfusates from Stimulated Human Skin

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THE PATTERN of the painful response which succeeds the intradermal injection of histamine is as follows: on injection there is an immediate sensation of pain which quickly disappears only to return after a short interval and continue for varying periods of time. The intensity of the response and its duration are directly proportional to the concentration of histamine. The interval between the immediate and latent response varies inversely as the concentration (1, 2).

This study concerns itself with the responses elicited by perfusates of human skin that have been subjected to various forms of stimulation. It has already been demonstrated by biological assay on the guinea pig ileum that such perfusates resemble histamine closely (3, 4). Fifteen subjects (medical, dental and pharmacy students) had tissue-paper-thin slices of skin removed from their arms. Preparations were made by a method described previously (3) and perfusates obtained after stimulating the skin *in vitro*. The respective subjects received injections of these perfusates as well as histamine.

METHOD

Care of Material. All glassware was washed in potassium dichromate sulfuric acid and rinsed well before autoclaving. Needles were placed in running water from 4 to 6 hours and then rinsed by forcing 10 ml. of distilled water through them. After sterilization and just before use, needles and syringes were rinsed in sterile saline three times. Histamine hydrochloride or phosphate was diluted in sterile saline made with chemically pure water. The skin was perfused with the same sterile saline as that used in making the histamine dilutions.

Preparation of Perfusates. Very thin skin slices of about three quarter inches in diameter were obtained by sterile surgical technique from the outer aspect of the arm with the use of a Smith-Ferris knife. The cut surface was wrapped around one end of a glass tube about 6 to 8 mm. in diameter, the

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edges of the tube being slightly everted. The graft was secured onto the tube by linen or silk thread so that it was water tight (fig. 1). The cavity of the cylinder was rinsed two to three times with 0.2 to 0.3 ml. of saline and after the last time the saline was allowed to remain. The skin was held over a small substage lamp just enough to warm the skin to about body temperature. The sample was removed after 3 minutes and 20 seconds of contact, by using a blunt needle and syringe and aspirating and expressing three times before the sample was finally gathered. Such washes were taken before and after the threshold levels of stimuli. The cylinder was shaken frequently during its contact with the saline.

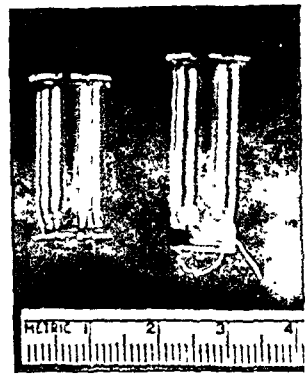

Fig. 1. GLASS CYLINDER with and without skin in place

Type of Stimuli. Tetanizing current by bipolar electrodes from a Harvard inductorium (2 dry cells in primary circuit): The threshold for pain was first determined for each subject. The skin was stimulated at the threshold level and at 4 or 2 cm. (primary from secondary coil). The electrodes were placed on the skin for 10-second intervals and then changed to another position until 20 sites were stimulated. The cylinder was shaken slightly between each stimulus.

Warm wire algesimeter (5). A loop of wire was heated electrically, varying the intensity by changing the resistance. The threshold level for each subject was obtained and the skin was stimulated for 10 seconds at each of 20 sites in the manner described above. A 2-mm. diameter steel rod was heated to white heat (in flame) and then applied to the skin for 2 to 5 seconds. The entire surface of the skin was thus charred (usually 10 sites).

Between each type of stimulus the cylinder was rinsed three times with saline. Too many rinsings are to be avoided, since the histamine will be washed out in this way.

Procedure for Testing. The subject was not informed of the nature of the experiment except that a small slice of skin would be removed and that perfusates as well as other substances would be reinjected into the skin. After the perfusates were all obtained, the subject was made comfortable in a reclining chair with a foot stool. All external noises or interruptions were at a minimum. The subject was told not to view the site of injection. The only instructions given were to record in his own words any sensation that might be experienced during and after the injections. He was given no information as to the sequence of the material injected.

By using the same syringe in which the perfusate was collected and by exchanging the blunt needle for a 27-gauge one, the needle was inserted as su-

perficially as possible into the skin, just burying the aperture. When pain from the insertion was over, about 0.01 of the perfusate was injected very slowly with minimum pressure to produce a 2- to 3-mm. wheal. The response of the subject was recorded and timed by means of a stop watch. A minimum of 3 minutes was allowed for each test. For comparison, varying concentrations of histamine were injected in the same way in the same arm. Saline injections were also made. During the course of injections, little questioning or prompting from the operator was indulged in, except as given below. At the end of each series of injections, the subject was questioned as to an overall comparison of the various materials injected without any reference to what the substances might be.

TABLE 1. IMMEDIATE PAINFUL RESPONSE ON INTRADERMAL INJECTION OF PERFUSATES FROM STIMULATED HUMAN SKIN

TYPE PERFUSATE	NO. OF SUBJECTS	NO. OF SAMPLES	PAIN ON INJECTION				
			0	+	++	+++	%
Saline	15	15	9	5	1	0	40
Wash onset	9	9	4	3	1	1	56
Warm wire threshold	7	7	1	4	2	0	86
Inductorium threshold	12	12	1	6	5	0	92
Wash after	6	7	2	1	3	1	71
Inductorium 2 to 4 cm.	5	5	0	0	2	3	100
Burn	11	11	2	3	1	5	82

RESULTS

Immediate Painful Response. Table 1 summarizes the results of the individual experiments, as well as the study as a whole. Not all skin samples were subjected to all the stimuli, and some of the subjects failed to voice pain on injection, because they stated afterwards that they expected some sensation at the time of injection. The gradations from 0 to 3+ refer to a comparison of the intensity of pain of the various samples injected in one individual, 3+ being reserved for some exclamation of pain. The results indicate a direct relationship between the degree of stimulus and intensity of the painful response. Thus, for example, in 5 of 11 subjects, injection of the burn fluid gave greater responses for this perfusate than for any other, as compared to no maximal response in 12 samples obtained from skin stimulated at threshold levels (inductorium). As a whole, there was a higher percentage of response from the perfusates of the stimulated skin than for the non-stimulated skin.

Latent Painful Responses. Following the immediate sensation there was usually a latent period devoid of pain after which a second painful sensation was manifest. As will be seen in table 2, this response was almost unanimous following all perfusates (statistically significant for the perfusates of stimulated

skin, with the exception of the warm wire, when compared with saline). After saline injections, only 6 of 17 samples initiated pain. The mean time of onset of the latent pain was roughly inversely proportional to the degree of stimulus. The calculations were based only on such samples in which a delayed response was manifest. The mean time of the duration of pain following saline was 0.24 minutes, and 3.4 minutes following burn perfusates. Another significant finding was that only one of 17 saline injections (6%) showed an augmentation of the latent painful response, whereas 13 of 15 (87%) of the burn perfusates were associated with an increase of pain (values of $p = <0.01$ for the inductorium (2–4 cm.) and burn perfusates when compared with saline).

The type of pain was described as pricking, sticking or burning. Such expressions as 'Like cutting my skin,' 'Like sticking with a needle,' 'Simulates a burn,' or 'Like a nettle sting' were frequently elicited voluntarily.

TABLE 2. LATENT PAINFUL RESPONSE TO PERFUSATES FROM STIMULATED HUMAN SKIN

TYPE PERFUSATE	NO. OF SUBJECTS	NO. OF SAMPLES	LATENT PAIN							
			No. +	% +	Value for P	Time Onset Seconds Mean[1]	Duration Minutes Mean[2]	No. Increase	Increase	Value for P
									%	
Saline	15	17	6	35		34	0.24	1	6	
Wash onset	11	11	10	91	0.02–0.01	25	2.0	5	45	0.05–0.02
Warm wire threshold	7	7	7	100	0.02–0.01	36	2.1	2	33[3]	0.50–0.30
Inductorium threshold	14	16	15	94	0.01–0.001	27	2.35	8	50	0.02–0.01
Wash after	6	7	6	86	0.10–0.05	15	2.0	2	29	0.50–0.30
Inductorium 2 to 4 cm.	10	12	12	100	0.01–0.001	23	2.38	8	67	0.01–0.001
Burn	13	15	15	100	<0.001	19	3.4	13	87	<0.001

[1] Considering only those samples giving a response. [2] Considering all samples. [3] 2 of 6 samples.

The local reaction following the injection of the perfusates greatly resembled those produced by histamine injections. Thus, there was central whealing surrounded by zones of hyperemia. Pseudopods were present in 3 of 11 samples (27%) of the 2- to 4-cm. inductorium perfusates, and in 13 of 15 (93%) of the burn fluid. The mean of the diameters of the area of hyperemia was one cm. for the threshold stimuli, 2 cm. for the inductorium (2–4 cm.) and 3 cm. for the burn fluid.

Histamine Equivalents. Histamine in dilutions of 10^{-10}, 10^{-7} and 10^{-5} was injected into the same arm as were the perfusates. In evaluating the histamine equivalents the following points were considered for each subject individually: the character of the response, the local reaction (size of erythema and presence or absence of pseudopods) and the immediate and latent components of pain. Each subject was questioned immediately after the experiment as to whether

or not there was a difference in the character of any of the injections. In every case the subject stated that the nature of the sensation was similar for all injections, but the intensity and duration varied.

A consideration of all of the above factors was involved in the construction of table 3. From this table it is noted that there is a direct relationship between the intensity of stimulus and the histamine equivalent. Threshold stimuli yield perfusates with histamine equivalents of between 10^{-10} and 10^{-7}, whereas following burning, the histamine equivalent was between 10^{-7} and 10^{-5}: 75 per cent of the samples were equivalent to 10^{-5}.

Other Sensations Following Injection of Perfusates. Itching was noted following the injection of 6 of the 15 burn samples and in 4 of 12 of the inductorium (2–4 cm.) samples. Cold, warm and pressure sensations were recorded to a lesser degree; the incidence and nature of such reactions will be considered in other studies.

TABLE 3. HISTAMINE EQUIVALENT OF PERFUSATES FROM STIMULATED HUMAN SKIN

TYPE PERFUSATE	NO. OF SUBJECTS	NO. OF SAMPLES	HISTAMINE EQUIVALENT			
			0	$\pm 10^{-10}$	$\pm 10^{-7}$	$\pm 10^{-5}$
Saline	15	17	11	6	0	0
Wash onset	11	9	1	7	1	0
Warm wire threshold	7	6	0	3	3	0
Inductorium threshold	14	15	0	9	6	0
Wash after	6	6	1	2	3	0
Inductorium 2 to 4 cm.	10	12	0	4	3	5
Burn	13	15	0	0	6	9

DISCUSSION

The similarity between the objective and subjective findings following the intradermal injection of perfusates of stimulated skin *in vitro* and histamine is striking. That such perfusates are histamine or histamine-like has been shown by the following biological assays (3, 4): *a*) the perfusates contract the guinea pig ileum in an atropinized bath; *b*) they are neutralized by histaminase; *c*) they are heat stable in acid and heat labile in alkaline solutions, *d*) they are dialyzable through a cellophane membrane; and *e*) action on the guinea pig ileum is prevented by the antihistaminic thymoxyethyldiethylamine (3, 6)[1].

The immediate painful response is probably dependent upon the proximity of the chemical stimulus to the specific pain receptor points, and may account for the absence of pain following injection of some of the stimulated skin perfusates. Since injury of the skin such as follows insertion of the needle or cutting is followed by the liberation of histamine, the pain responses, albeit in low percentage, following saline or the washes are understandable.

[1] Thymoxyethyldiethylamine was supplied to the author in 1938 by Dr. Fourneau of Paris.

The warm wire algesimeter at threshold levels of stimuli will give only the second component of the double pain response in human subjects, but perfusates of such stimulated skin (20 sites of stimulation of 10 seconds each) gave an immediate response as well in 11 of 12 samples. In each individual subject the intensity of the immediate pain produced by the perfusate was directly related to the severity of the stimulus of the skin *in vitro*. The latent response is most likely the result of the summation of many subthreshold stimuli effected by this histamine or histamine-like substance diffusing into the skin. Such substances are liberated upon stimulation of the skin, whether or not they be of threshold or even subthreshold levels. Histologic sections have failed to reveal any changes in the skin following threshold stimuli (3). The latent pain in many instances increased after it was once initiated. This is evidently related to the histamine concentration, which in turn determines the number of pain points activated. In 13 of 15 samples of burn fluid, an increase in pain was registered. This was also true following histamine injections. Such an augmentation was noted in 34 of 41 injections of histamine in 10^{-5} dilution and in 14 of 47 injections of 10^{-7} dilution.

The duration of the painful response is likewise dependent upon the concentration of histamine or a histamine-like substance. Hypothetically, the time of onset of the latent response is dependent upon the number of subthreshold stimuli initiated. The higher the number at one time, the shorter the time of onset. Since the burn fluid contained the highest concentration as well as the largest amount of histamine, the time of onset of the latent pain was the shortest. In 2 of 15 samples there was no let up in the pain following its onset on injection.

The skin contains histamine in the approximate concentration of 1:50,000 dilution (7). This concentration could well account for any magnitude of cutaneous pain. As has been shown, the pain response to burn fluid can be very intense, yet it corresponds to histamine concentrations between 1:10,000,000 to 1:100,000, but more commonly the latter.

A limited number of experiments were made by using such stimuli as pinching (with sharp pointed forceps 30 times), pricking with a needle (50 times), or chemically irritating with xylol. All such perfusates gave responses which simulated the threshold values or slightly above.

This study indicates that physiological stimuli as well as pathological ones causing injury liberate histamine or a histamine-like substance which is responsible for the mediation of immediate and latent painful responses. This is in sharp contrast to the views expressed by Lewis (7), who denies that histamine or a histamine-like substance is concerned with pain at any level. He agrees with those before him (7) that some chemical substance is liberated in gross-tissue damage which may account in part for the latent painful response only. Again, he is emphatic that the substance is not histamine. Lewis explains

the immediate response by direct physical irritation of the specific pain points, and the secondary painful response by physiological stimuli as the result of varying conduction rates over nerve fibers of different diameters. The latent response as described in this study probably differs from the second component of the double pain response, since the time of onset of the former can be delayed for a mean of 16 seconds or more (slow fibers have a conductivity of approximately 0.5 to 1.0 meters per second, 8). On the other hand, the possibility exists that normally there is greater efficiency and proximity of the mediating substance and the pain receptor cells, which would lessen the time of onset of the latent painful response as described above.

CONCLUSIONS

Perfusates of skin stimulated *in vitro* when injected intracutaneously into human subjects produce local reactions and a pattern of painful response similar to that of histamine injections. The pain has an immediate and latent component. Its intensity and duration are directly related to the degree of stimulation. The interval between the two components of pain is inversely proportional to the stimulus. This evidence favors the theory that histamine or a histamine-like substance is the chemical mediator for cutaneous pain.

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Electric Current Transients through the Human Body[1]

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THE PASSIVE electrical characteristics of tissue have generally been studied by the frequency response method of analysis. A network of two resistors and one condenser (fig. 1*A*) has often been proposed as giving an electrical response equivalent to that of the tissue studied (1–8). However, some more complicated and different networks have been proposed, such as a two condenser-four resistor one by Lullies (9). Cole (10) has developed the method of the complex plane locus for frequency dependent impedances. This method includes the possibility of recognition of the condenser element in figure 1*A* as itself having frequency-dependent impedance.

Another method of study of the passive electrical characteristics is through the observation of the transient of current following the sudden application of a constant voltage. Gildemeister (11–13) and Einthoven and Bijtel (14) studied such transients with string-galvanometers. However, the frequency response of the galvanometer is much too poor to follow the rapid transients observed in tissue with any accuracy. Strohl (15) and Hozowa (16) made use of the ballistic galvanometer to give a point-by-point plot of the transient.

METHOD

In the present work, a rectangular voltage wave was supplied by a DC amplifier to two electrodes on the skin. The electrodes, of Crook's metal, were covered with Redux electrode paste and fastened by straps. The indifferent electrode had a surface of 150 cm. and the stigmatic, 24 cm. A voltage across a small resistance in one of the leads is proportional to the current. This voltage is amplified by a cathode-ray oscilloscope and the current pattern is observed on the oscilloscope screen. A repetitive wave is used so that the current pattern can be synchronized with the sweep and photographed for later analysis. The duration of the pulse is much longer than required for the transient to die away and therefore no distortion is introduced by the repetition.

It would be expected that, following a sudden application of a constant voltage, V, the current through the network in figure 1*A* would be large at

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[1] This work was a project of the Baruch Center of Physical Medicine, which carried the expenses involved.

the start, decreasing exponentially to a final steady value. The resistance, R_1, would limit the maximum value of the initial surge of current which charges the condenser, C. The condenser should charge exponentially through R_1 to a final steady state voltage equal to that across the resistance, R. The steady state current is given by ratio $\frac{V}{R_1 + R}$, since no more current flows into the condenser. The final voltage across C will then be $V \times \frac{R}{R_1 + R}$. Therefore, one would expect to be able to subtract the steady state value of the current from the transient and obtain a simple exponential decrease in this net current with time. In other words, the log of the net current vs. time should yield a straight line.

Proposed Analog Network. The transients obtained in this work were of the general shape expected, but, on the semi-log analysis, did not yield the expected straight line. Neither was it possible to match the whole transient through the body with a dummy network of the type in figure 1*A*. However, it was observed that the curved line found on semi-log analysis was the sum of

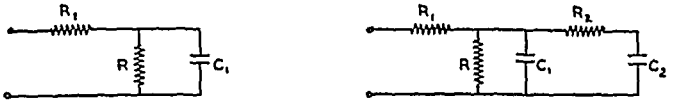

Fig. 1. A (*left*): single R-C network; B (*right*): double R-C network.

two straight lines; their slopes differed by a factor of approximately 6. This indicated that two *RC* combinations were required for an equivalent dummy network. The network shown in figure 1*B* gives a transient similar to that observed through the human body. The constant R_2C_2 (averaging about 180 μsec.) is approximately $6 \times R_1C_1$ (averaging about 30 μsec). Hozowa (16) performed the same type of analysis on the ballistic galvanometer transient curve and also found a deviation from a straight line. This he interpreted as a variation with time of one of the elements (C_1) of the simple network of figure 1*A*.

DISCUSSION AND RESULTS

It is necessary to consider the difference in the frequency-response and the transient methods of analysis. The frequency-response curve is simply a plot of the relative magnitude of current passing through a network as the frequency of a sinusoidal wave is varied. The phase angle lag of the current with respect to the voltage must also be taken as a function of frequency to obtain a complete picture. The measurements are usually taken point-by-point at several selected frequencies. It is often found that on biological objects,

when the points are rechecked, the values do not reproduce too well. Frequency-response curves taken by us on single and double *RC* networks with the time constant values set at average values as observed in human tissue are shown in figure 2*A*. The phase angle plot is not shown. The general shape of the two curves is similar. In biological work, uncertainty of the points would approach

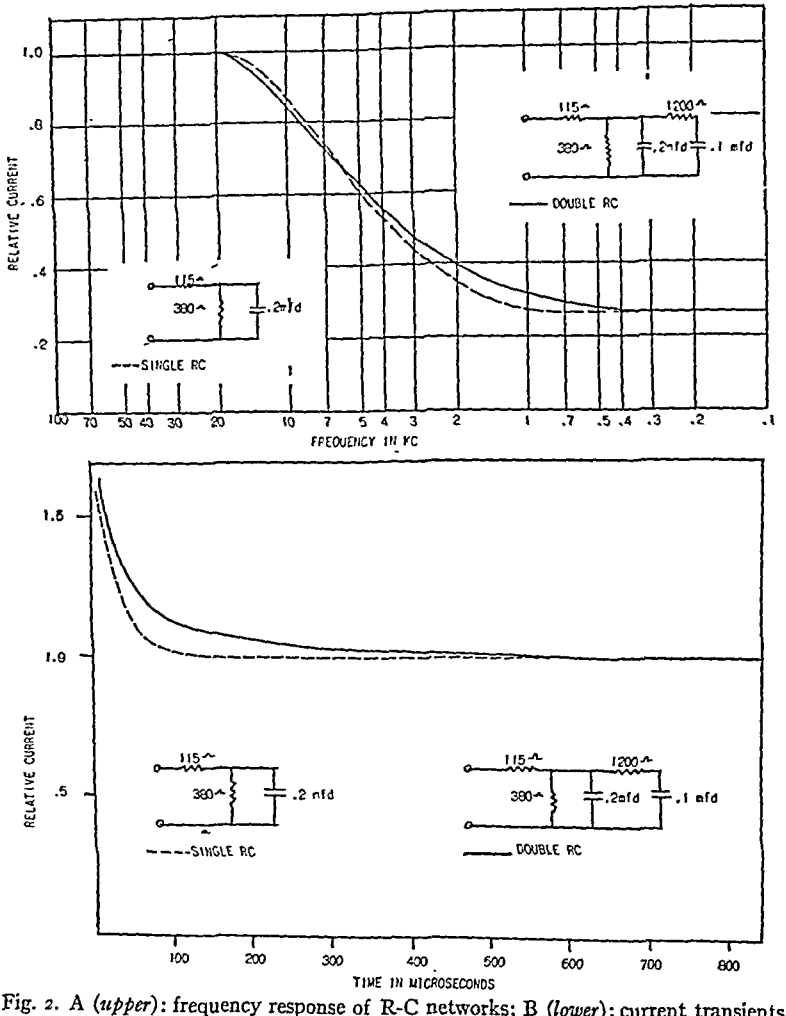

Fig. 2. A (*upper*): frequency response of R-C networks; B (*lower*): current transients through R-C networks.

the percentage difference of the curves. Thus, it would be difficult to say which type of network is equivalent to tissue frequency response. The transient responses for the same two networks are shown in figure 2*B*. The difference in the two transient responses becomes quite clear on the semi-log analysis shown in figure 2*C*.

Current transient analyses for human subjects are quite similar to that for the double *RC* network. A typical subject analysis is shown in figure 3. The straight lines have characteristic slopes which have been designated α and β as indicated in the figure. In practice, the α slope is obtained by extrapolating the straight portion towards the end of the transient back to zero time. This is subtracted from the transient and the remainder plotted. The remainder is the straight line of slope β. It is of interest to note that while the steady state current (proportional to the *DC* conductance) may vary widely from subject to subject and under various conditions for a single subject, the slopes α and β remain quite constant. It is easily seen from figures 2C and 3 that, as the net current becomes small with increasing time, great care becomes necessary

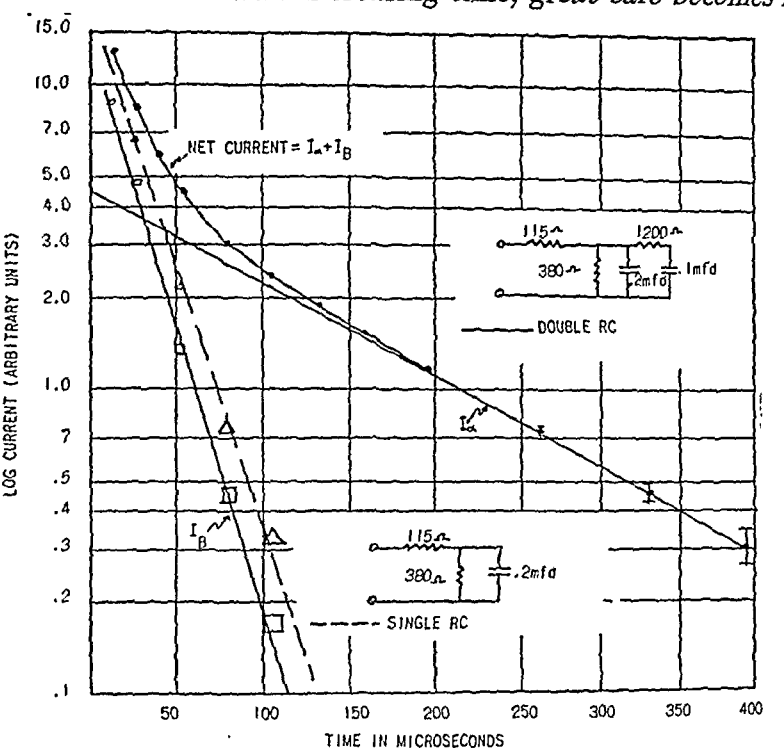

Fig. 2C. Analysis of current transients through R-C networks.

in reading accurately the current values. The percentage error due to the finite cathode ray trace width and in estimating fractions of the grid divisions (picture is taken with transparent grid pattern across face of cathode ray tube) becomes increasingly large as the transient current approaches the steady state value. When the α slope straight line is extrapolated back to zero time, any error in properly choosing the slope will, of course, affect the slope of the second straight line, β. The gradually increasing error in the points from which α and β are taken is indicated in figure 3. It is difficult to estimate the percentage error involved in the determination of the slopes since the minimum *net current* value plotted varies considerably and usually in proportion to the variation in steady state current. Sample photographs were studied and it was found that with the poor readings, errors of approximately ± 10 per cent could

be introduced. However, different persons in analyzing the same transient photograph agreed within 5 per cent on the slopes. An electrical computer has been considered for improvement of the accuracy. The steady state current should be measured with good precision and subtracted from the transient current; this is feasible in a repeating wave. The logarithm of the net current would then be taken and the semi-log transient analysis could be presented on the oscilloscope screen for photographing. The slope α would then be determined easily and less error in the value of β would be introduced.

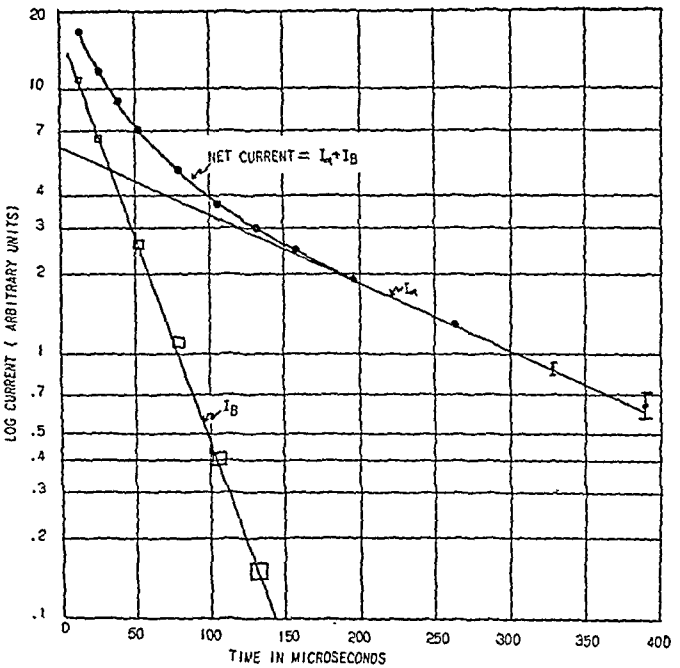

Fig. 3. TYPICAL CURRENT transient analysis

It was undertaken to determine what, if any, factors influenced the slopes α and β of the characteristic straight lines. Several factors were varied and typical results are tabulated in table 1. A few preliminary experiments in stopping circulation to a limb with a blood pressure cuff gave consistent increase in α of about 15 per cent. After circulation was restored and hyperemia (17) resulted, α was observed to decrease below the initial control value. This decrease was quite variable with time after the pressure was released and with different subjects in accordance with the variation in blood flow in the hyperemic state in the reference quoted. The electronic computer would be invaluable in a study such as this where considerable data is desired on the variation in α over a short period of time. It was also found that when the indifferent electrode was placed on the tongue, a single straight line only was observed. It had the characteristic α slope.

Instrumentation and Limiting Factors. A block diagram of the circuits used in this work is shown in figure 4. A variable frequency generator of the multivibrator (18) type is employed. By taking the derivative of its output a sharp pulse is obtained at each cycle. This pulse is used to trigger a uni-vibrator producing a rectangular pulse of variable time and amplitude. A direct current amplifier with both voltage and current feedbacks is provided to give rectangular waves of either voltage or current. The cathode ray oscilloscope (CRO) can be connected to monitor the output wave form or transient involved. In the work reported here, voltage feedback is used and the current transient observed by connecting the CRO across the low resistance in series with the subject or dummy. When the amplifier was designed, it was not

TABLE 1

VARIABLE	RELATIVE VALUES	PERCENTAGE DIFFERENCE α	β
Frequency	360 to 270 cy/sec.	+6	+6
Voltage	3 times	±4	±5
Steady state current	3 times	±4	±5
Pulse time	3 times	None observed	
Electrode size	24 to 7 cm.	−11 Same current	+25
		−27 Same voltage	+25
Limb	Left arm to right arm	−14	+7
Subjects	4 male	±12	±15
	4 female	±15	±18
	Ave. of 4 males and ave. of 4 females.	±11	±18
Current path length	Small electrode from same limb as indifferent to opposite limb	−18	−33

Where standard conditions are varied, the standard 'to' the new value is quoted and percentage change indicated. Where no standard of reference is used, a maximum ± percentage change is quoted.

known that such a heavy current surge would be experienced at the start of the transient. The feedback incorporated was not adequate to completely take out all the lowering of the voltage; it is reduced not more than about 10 per cent at the start and is back to within 3 per cent of its final value within 70 μsec. This does not affect our results appreciably since in a test experiment a single *RC* gives a straight line from a few microseconds and since a subject's transient is not generally completed until about 500 μsec. With the oscilloscope used (having a flat frequency response to only 100 kilocycles), the pulse amplifier employed was probably adequate with its rise time of less than 7 μsec. However, in order to study the transient at a few microseconds, an oscilloscope with much better frequency response is required, along with a faster amplifier incorporating more feedback. Therefore, it is clear that the

statements made here with regard to the transients refer to the period after the first few microseconds. The network proposed as giving the equivalent response is subject to the same restriction. Another factor to be considered is that for some persons the surge limiting resistance, R, is small—say, only 5 times the series resistance required for current measurements. This will particularly affect the current transient at very short times and will also introduce an error of about 20 per cent in the observed value of β. Higher amplification in the oscilloscope will aid in eliminating this limitation.

On many analyses, the value of the current at the shortest time regularly used (14 μsec.) was slightly higher than the sum of the two straight lines. This hint that for very short times (10–14 μsec.) the proposed network is not completely adequate has been borne out by a few bridge experiments in which the current through the subject and dummy network were directly compared. The difference can be observed with the present instruments, since the oscilloscope is being here used as a null indicator rather than being relied on for the true

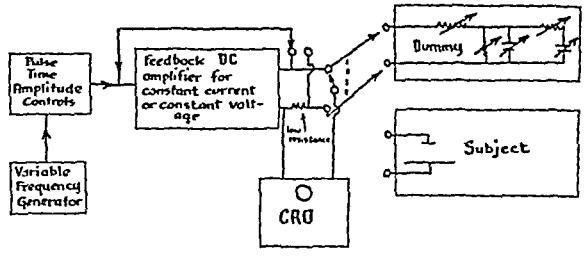

Fig. 4. Block diagram for current and voltage transients

wave shape. The bridge experiments were not used in the routine experiments because of the interaction of the values of the dummy elements, i.e. the values of four of the elements contributed to the size and shape of the transient. This requires considerable juggling of the values of R_1, C_1, R_2 and C_2 in order to obtain the desired balance.

It is also true that by the present method a longer decay time than R_2C_2 would not be detected due to the limitations already mentioned with respect to the accuracy in obtaining the slope.

Correlation With Physiological Data. It has long been thought that there should be a simple connection between the passive electrical nature of tissue (studied by impedance methods) and electrical network analogies derived from excitation studies. The shape of the current transient is reminiscent of the strength-duration curves in nerve and muscle excitation. In the current transient work, a very small voltage was used (only enough to give a good sized pattern on the oscilloscope screen); thus, the electrical stimulus involved was far below threshold. A few preliminary experiments have been performed to

see if a direct relationship existed between the current transient and the strength-duration curve for nerve. A small electrode was secured over a motor point on the forearm and both types of data taken. It was found that the constant current strength-duration curve (standardly used in physiology) could be matched by simple operations on the data from the constant voltage current transient. The constant voltage strength-duration curve might then be directly proportional to the current transient. However, the pulse available from this amplifier was not sufficiently rectangular at the very short times required (a few microseconds) to get sufficiently accurate results for comparison.

SUMMARY

The passive electrical characteristics of human tissue have been studied by the method of the current transient associated with an abrupt voltage change. Photographs are taken of the transient pattern on an oscilloscope screen and are analyzed for characteristic exponential decreases in current with time. Two characteristic exponential current decay rates were found and a network giving the same type of transient is presented. The decay rates are shown to be relatively constant from person to person. A table is given to show the effect of variation of several factors involved.

It is postulated that a correlation between physiological data of nerve and muscle excitability and their passive electrical characteristics may be found by the transient method.

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Effects of Helium and Altitude on Respiratory Flow Patterns

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IN THE PREVIOUS STUDY of breath flow patterns in men breathing oxygen at ground level and at 30,000 ft. simulated altitude (1), it was shown that significant changes in velocity and timing of breath phases resulted from changes in density of the respired gases. Since rarefaction is but one method of changing density, it was felt that further analysis of the influence of this factor would be afforded by the use of a light gas such as helium for pulmonary ventilation (2). In studies on lung ventilation by Dean and Visscher (3), the effect of density, studied by means of such gas mixtures, could not be differentiated from the possible effect of accelerated diffusion which favors the establishment of equilibrium concentrations of both oxygen and carbon dioxide in helium-rich gases of the alveolar space. Since up to 30,000 ft. pressure-altitude the effects of rarefaction on diffusion within gases are negligible, a separation of these factors may be made.

Accordingly, series of tests were set up to measure breath velocities in the same subjects breathing oxygen at ground level, oxygen at 30,000 ft. simulated altitude, and 20 per cent oxygen in helium at ground level. For purposes of correlation a series of structural and functional tests were made on each subject as outlined below. Special efforts were also made to improve the analysis of the breath velocity pattern, especially with regard to the initial phases of acceleration which we felt to be sensitive to the flow resistance factor. Finally, an attempt was made to find internal correlations of the velocities of various phases of the breath flow.

MATERIAL AND METHODS

Twelve Navy recruits who had volunteered for low pressure indoctrination were obtained through the courtesy of the Naval Medical Research

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Institute. The staff of the latter screened these subjects medically with routine physical examinations and trial low pressure exposure. Independent physical examinations and physiological tests were then made by our own staff. Data from the latter are presented in table 1. They indicate a physically homogeneous population.

The primary data collected on the subjects before any breath velocity tests were made are: age; height; weight; patellar and calcaneus reflex patency; blood pressure, seated; pulse and respiratory rate before, immediately after, and two minutes after a standard stepping exercise according to the method of Behnke *et al.* (4); maximum minute volume (5); breath

TABLE 1. DATA FROM PHYSICAL EXAMINATIONS AND PHYSIOLOGICAL TESTS

NO.	AGE	HT.	WT.	WT./HT.	SURFACE AREA	BLOOD PRESSURE	PULSE INDEX[2]	RESP. INDEX[2]	VIT. CAP.	BREATH HOLDING TIME	MAX. MIN. VOL.	pN_2 ALV. AIR[3]	pO_2 EXHALED AIR	A_r[4]	V_r[5]
	yr.	*cm.*	*kg.*		m^2	*mm. Hg*			*l.*	*min.*	*l.*	*mm.Hg*	*mm.Hg*		
13	19	182	72	.39	1.92	120/67	57	14.5	4.51	1.33	103	594	95	73.2	51.2
14	19	178	72	.41	1.89	118/65	70	12.0	4.78	2.00	102	590	101	68.4	52.7
15	19	170	82	.48	1.95	116/71			4.87	1.25	93	596	110	64.4	52.2
16	18	170	62	.36	1.72	103/50	63	16.5	4.29	1.18	84	591	105	70.0	55.3
17	19	183	80	.44	2.02	108/70	66	14.0	4.34	0.78	93	596	115	73.0	55.5
18[1]	19	179	78	.43	1.96	116/59	64	15.5	4.20	0.98	103	589	113	62.8	47.7
19	19	175	73	.42	1.87	108/62	58	15.0	5.35	1.19	90	594	111	68.5	53.4
20	18	176	79	.45	1.95	109/72	54	12.0	4.65	0.85	99	590	104	67.8	52.2
21[1]	19	184	77	.42	2.00	111/60	52	14.0	4.67	1.22	134	598	110	64.9	44.8
22	19	181	81	.45	2.01	117/74	57	15.5	5.64	0.98	73	588	118	80.0	64.8
23[1]	19	179	73	.40	1.90	108/65	59	13.5	4.73	1.22	116	595	107	75.7	62.1
24	18	179	74	.41	1.90	124/75	58	14.0	4.55	1.30	86	596	106	69.6	50.8

[1] Subjects omitted from table 2. [2] After Behnke (4); see text. [3] Mean of 2 alveolar air samples. [4] After Hurtado and Fray (6); A_r = 100 (max. expiratory area/max. inspiratory area). [5] After Hurtado and Fray (6); V_r = A_r (max. expiratory ant.-post. diameter/max. inspiratory ant.-post. diameter).

holding time; vital capacity by the method of Hurtado and Fray (6); pO_2 of exhaled air using the Pauling tensimeter and the continuous sampling technique of Rahn *et al.* (7); pN_2 of two alveolar air samples analyzed by the Scholander technique (8); 14 x 17-inch chest roentgenographs, and anterior-posterior chest diameters (6); past medical history; present clinical complaints; cigarette and alcohol consumption; pre-Navy occupation; education; and birthplace.

From some of these data indices of several types were calculated for the purpose of correlation with breath velocity test data. The linear density calculation (weight per unit height) discussed by Behnke (9) was made for correlation with altitude responses. The cardiac fitness (pulse) index intro-

duced by Behnke *et al.* (4) was calculated according to both formulae given by him but only the values for the simplified one are presented here; $([Pa_1 - 70] + 3[Pa_2 - Pb]$ and $[Pa_1 + 2Pa_2]/4$, where Pb is pulse beats per minute before exercise, Pa_1 same immediately after, and Pa_2 two minutes after exercise). An arbitrarily chosen similar (respiratory) index was calculated for the respiratory rates recorded in the same test. The lung area ratio (A_r) and volume ratio (V_r) were calculated from the chest roentgenographs and were made in accordance with the technique used by Hurtado and Fray (6). In connection with those tests susceptible to alteration by motivation, an effort was made to incite competition between the subjects, e.g., maximum minute volume, vital capacity, etc.

The breath velocity studies were carried out in a decompression chamber both for low pressure and normal pressure tests. The recording technique followed that described in a preceding paper (1). The instrument used for recording as well as the breathing circuit in which it was incorporated has been described elsewhere (10). In essence the subjects breathed through the flowmeter in a closed circuit which included a modified Benedict-Roth type spirometer with large directional rubber check valves and a carbon dioxide filtering bed of very low resistance.

Ascents were made by two subjects at a time and were repeated after about 2 weeks. Subjects with acute upper respiratory infections were excluded from the tests and obviously distorted responses also were responsible for the occasional elimination of data.

The general plan of the experiment permits a comparison of data taken in oxygen at ground level pressure, in oxygen at a pressure-altitude equivalent to 30,000 ft. and in helium-oxygen mixtures (80, 20% resp.) at ground level pressure. All subjects were given each test, the comparisons between oxygen at ground level versus oxygen at altitude and versus helium-oxygen at ground level being made on different days. Thus comparisons between the effects of rarefaction and of helium-oxygen are temporally indirect.

The breath velocity records were analyzed for the same data presented in our previous paper but, in addition, the initial acceleration (Ia) was divided into two portions (Ia_1 and Ia_2) in order to show abruptly changing accelerations in some records. This was done because the change in slope of the velocity trace as the velocity first rises seems to be different for different subjects, and this difference may be an index of what has been described by Silverman (11) as 'damping' under certain conditions. The detailed study of acceleration data also has been urged by Gukelberger (12) who applied it to the differentiation between the mechanics of inspiration and expiration.

The measurement of accelerations was made by reading the angular slope on a transparent protractor designed for this purpose and translating these data to liters/minute/second by calculation. It is necessary to note here

tion are more enhanced at rest than following exercise, while the accelerations are less uniformly enhanced than are the maximum velocities, particularly at rest. The length of the expiratory cycle is significantly changed by He-O_2 in both rest and exercise, but a significant increase in post-expiratory pause (*Eps*) is found only in the 12-subject analysis as referred to above. This indicates that plateau velocities are sustained in He-O_2 somewhat better than in O_2 under these conditions. This is to be noted particularly at rest during expiration. It is notable that in exercise there is evident a density effect in many items, particularly in the post-expiratory pause.

The data on identical items in *series B* indicate a change in response to rarefaction of the atmosphere similar to those occurring with He-O_2 but of lower magnitude and statistically not significant. In fact, the nine subjects studied had difference values varying from those reported in our preceding paper (1), although they were in some instances greater (*Eps, Es, Ips, Is, Imf*). The variation between subjects coupled with the smaller number of subjects contributed heavily toward the lack of statistical significance.

It is apparent from these considerations that average values are not a satisfactory means of demonstrating such phenomena to their best advantage. Although we have attempted classification of our subjects according to other clinical data, it has not been possible to obtain high correlations with the breath velocity data.

An analysis of the normal incidence of *Eps* in O_2 and the change induced by He-O_2 and altitude in the 12-subject group indicates that: one individual showed no pauses under any condition; five showed none in the altitude series; four in He-O_2 and two at altitude gained a pause although normally they showed none; one in He-O_2 and three at altitude gained an increment over their values in O_2 at normal conditions; four in He-O_2 similarly showed a decrement; and two in He-O_2 and one at altitude showed no change.

This type of distribution of incidence of change seems characteristic of all the items measured in this study. Correlations were low among the breath velocity items and among the clinical test items. There were no correlations evident between items in the two categories.

DISCUSSION

The search for correlations in these data was made in the hope that clues to significant factors might be established for further work on individuals with abnormal pulmonary conditions. It was not unexpected that the clinical data with such a very small range should fail to show correlations, but the breath velocity pattern data were expected to yield some interrelationships which might be used in predicting changes in specific portions of the breathing act. It must be concluded that the controlling factors are numerous and independent.

It was impossible to portray the 'average' patterns in this series of data, and we feel that the tentative explanations for areal differences in the velocity patterns previously given (1) are inapplicable in the face of the obviously independent response of the several variant items.

The most interesting change in breathing which both rarefaction and helium dilution bring about is in the incidence and duration of interphasic pauses. As discussed in our report of the effects of altitude on the breath velocity pattern (1), a significant lengthening of the post-expiratory pause results from a reduction in the density of the respired gases even though this is calculated on the basis of average values which tend to obscure the individual reactions.

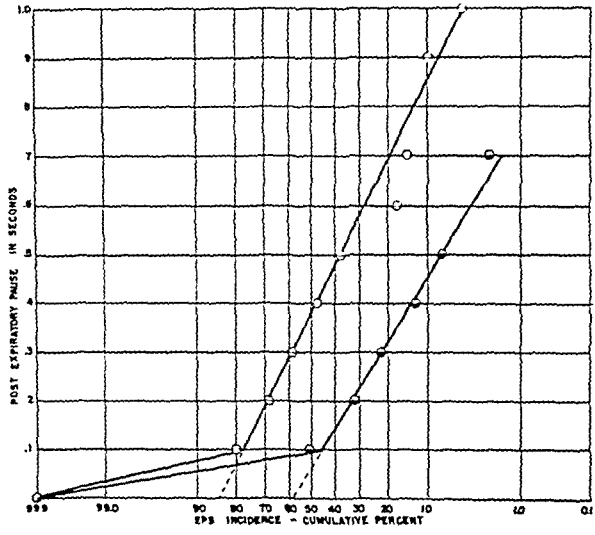

Fig. 1. CUMULATIVE INCIDENCE of *Eps* at various durations grouped in 0.1-second intervals. Half shaded circles = ground level, open circles = altitude Pooled data on 41 subjects from this and the previous publication (1). See text.

If frequency of incidence of *Eps* is plotted against duration as a cumulative percentage, as in figure 1, it can be seen that the data[1] are reasonably linear but oriented in such a fashion as to meet the abscissa at about 50 per cent for the ground level and at 80 per cent for the altitude group. One may assume from the linear character of the positive data that the distribution is normal. The relatively small change in slope with rarefaction is an indication that an arithmetic displacement of all groups is effected, and that the arbitrarily labeled zero category is in reality normally distributed into the negative quadrant of the plot. With a normal distribution oriented in this fashion it is then pertinent to inquire into the possible causes for deviation of the zero category data and the meaning of the direction of the trend into the negative quadrant of the plot.

[1] Pooled data on all altitude experiments on 41 subjects.

The latter implies that the pause is caused by some function of respiration which, unlike time (i.e. duration) can have a negative aspect. Perhaps the most reasonable factor is the CO_2 or O_2 tension or both, in the circulating blood as related to the point of adequacy for metabolism. One may account logically for the opposite reactions of different individuals to the stimulus given in these experiments without denying the basic assumption that individuals are normally distributed with regard to the ventilatory ability and that they respond essentially with an increased pause when other factors permit.

All the pause data in both He-O_2 and at altitude show a similar distribution of incidence although the small sample involved is inadequate for analysis. The testing of the hypothesis regarding the primary physiological factor and its evaluation is possible only through animal experimentation under conditions of controlled breathing. Such experiments are being undertaken currently.

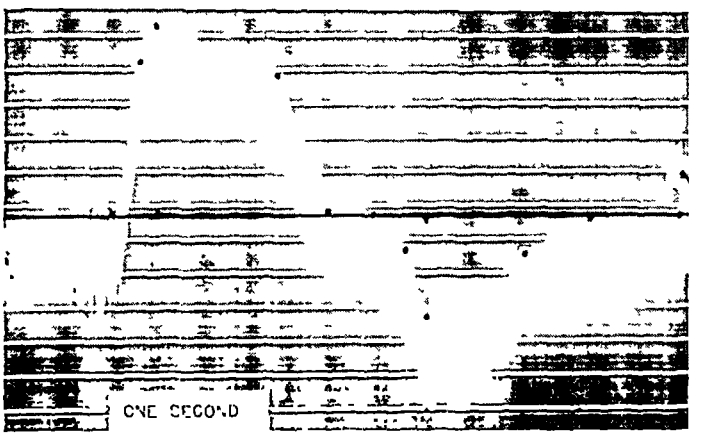

FIG 2. SAMPLE TRACING of one respiration of *subject 13* at rest breathing helium-oxygen Time seconds; horizontal lines 5 mm apart Ink marks show reference points; inked line indicates zero position of flowmeter; inspiration is above this baseline, expiration below. For further explanation see (1).

The mechanism resulting in post-expiratory pauses as intimated here and in our previous paper (1) rests on changes in density since this is the only significant physical change known to have been effected by ascent. We feel that the altitude effect should be expected to be smaller, as observed here, than the helium-oxygen effect because the acceleration of diffusion of CO_2 and O_2 in helium within the alveolar space, mentioned by Dean and Visscher (3), is lacking in rarefied oxygen at the pressure used. This supports their suggestion that this factor may be credited, in part, with the observed improvement in respiratory exchange in the therapeutic use of such mixtures in asthmatic patients rather than the negligible decrease in resistance to flow. They did not consider, however, the contribution of mass or density per se in their analysis and our altitude tests show that this is a significant factor.

While the incidence of perceptible post-inspiratory pauses is very low in these data, a change similar to that observed in post-expiratory pauses with decreased density, is effected. The existence of such pauses has been ques-

tioned (13), but there is no physiological basis for denying the possibility of their occurrence in some normal individuals (see fig. 2). In contrast to the passive post-expiratory pause the hypothetical basis for a density effect on the active post-inspiratory pause is not readily drawn.

A superficially plausible explanation of this phenomenon in our observations derives from those of Fleisch (14) in which oscillations in the breath velocity were found to occur regularly under certain conditions of relief from occlusion or resistance. If the breathing of an unaccustomed light gas can be held to similarly affect the reciprocal balance of the pulmonary musculature then such oscillations might be expected in certain individuals at any point in the breath pattern. Although we have observed them in our recorded breath patterns a check on this item in each instance where post-inspiratory pauses were reported shows that only a few of the cases in question may be involved with such oscillations. The failure of previous investigators to demonstrate this phenomenon and the denial that it exists 'normally' (13) stems most likely from the inertial or hysteritic deficiencies of the flow measuring instruments employed.

The questions raised by the data of these experiments are of such a character as to require an intensive analytical approach through animal experimentation. Such work is being planned, in particular with controlled observation of the innervation of the respiratory mechanism.

SUMMARY

Breath velocity data obtained in rest and exercise breathing either oxygen at 30,000 feet simulated altitude or helium-oxygen mixtures of the same density are compared to those obtained breathing oxygen at ground level. Decreased density either by rarefaction or gas mixture causes an increase in breath velocity and a hastening of the completion of both inspiratory and expiratory phases. A helium-oxygen mixture of density equal to that of oxygen at 30,000 feet altitude has a more marked effect than the latter. The facilitation of pulmonary ventilation introduces a post-expiratory pause in some individuals and lengthens it in those normally showing such a pause. Post-inspiratory pauses are observed to follow the same course but with a much lower incidence. Correlations between clinical indices of pulmonary fitness and breath velocity data in this selected normal population are essentially random.

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Determination of CO_2 Content of Mixed Venous Blood Entering the Lungs

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WE HAVE RECENTLY described a method of sampling alveolar air in which the dead space is cleared by gentle suction at the end of an expiration. The results agree closely with those obtained from Haldane-Priestley end-expiratory samples, and the method has an important advantage in that the taking of a sample does not disturb the subject. There is little variation in a series of estimations made on the same subject at short intervals (1). This technique has now been adapted to the measurement of the CO_2 content of gas mixtures approaching equilibrium with the mixed venous blood entering the lungs, and hence to an estimation of the CO_2 content of the mixed venous blood. It has obviated the conventional lung-bag system, and has thereby simplified the problem of mixing in the lungs.

APPARATUS AND PROCEDURE

The apparatus has been described in detail in a previous communication (1). A modification was made by the addition of an aperture at *B* (fig. 1), on to which a Douglas bag could be fitted (capacity unimportant) and into which a continuous supply of CO_2 mixture could be supplied from a cylinder. The bag was fitted with an expiratory valve to keep the pressure constant. This made it possible, by means of the rotating tap of the apparatus, to carry out the following procedures:

1) At the end of an expiration into room air the tap was turned through 270°. This closed the opening to room air at *A*, and opened *B* which communicated with the Douglas bag containing the known CO_2 mixture. During the course of this rotation the respiratory and instrumental dead space was automatically cleared by means of the previously-evacuated rubber bulb *C*. *2*) The tap was left at this position while the subject took two normal respirations from bag *B*. *3*) At the end of the second expiration the tap was turned back through 180°. In the meantime the bulb at *C* had been evacuated, so that at the end of this rotation the deadspace was cleared once more. *4*) Immediately after this an alveolar air sample was obtained by means of the sampling tube *H*, and then the tap was turned through a further 90° so that the subject could

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breathe room air. If the movements were carried out rapidly there was no interference with normal breathing, and the subject was not conscious of the procedure.

The experiments were all carried out on 5 subjects, in an air-conditioned room at a constant temperature of 76° and humidity 54 per cent. The experiment was repeated using various concentrations of CO_2 in the Douglas bag, and employing each concentration two or three times. Each experiment lasted only about one minute, and there was a pause of a few minutes between successive experiments.

In addition to the above, two or more samples were taken for the estimation of the arterial CO_2 tension, and expired air was collected for the determination of the CO_2 output. If the CO_2 tension of the inspired mixture is within

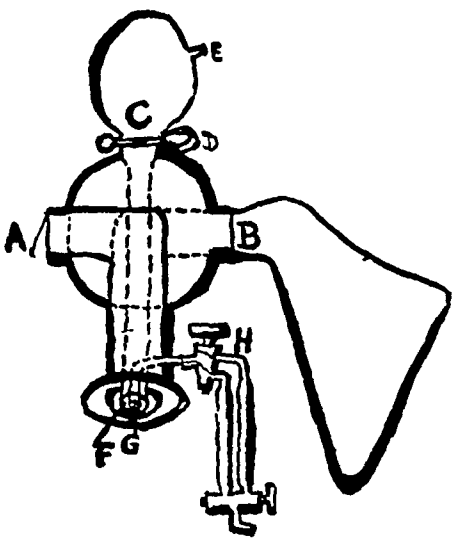

Fig. 1. *A*. INLET-OUTLET for normal breathing to room air. Suspended at the aperture is a piece of latex to indicate phase of respiration. *B*. Communication with Douglas bag containing CO_2 mixture. *C*. Rubber bulb of 180 cc. capacity which communicates by a separate pathway with the mouth, at *F*. *D*. Clip to close off bulb if required. *E*. Valve to facilitate evacuation of *C*. *F*. Lead to suction bulb. *G*. Lead to sampling tube. *H*. Sampling tube with two evacuated barrels.

some 10 mm. Hg of that expected in the mixed venous blood, the CO_2 content of the samples of expired air does not vary widely, and is presumably close to that of a gas in equilibrium with venous blood. We have attempted to identify this more accurately in the following manner. If one plots the difference between the CO_2 tension of the alveolar air and the CO_2 tension of the inhaled gas as ordinate against the CO_2 tension of the inhaled gas as abscissa, one finds, as Ewig and Hinsberg claimed (2), that the relationship of the two variables is approximately linear. We have found experimentally that this linear relationship holds good in the region of the x-axis; therefore at the point where the line crosses the x-axis, the value for the CO_2 tension of the alveolar air is the same as that for the CO_2 tension of the inspired gas.

The experiment begins with the clearance of the deadspace by suction at the end of an expiration, so that the gas then remaining in the respiratory system already has a CO_2 tension as high as the arterial level. One breath of the

mixture is then taken and expelled, and an opportunity is thus provided for CO_2 to diffuse from both the inspired air and the venous blood into the intermediate zone of air, and to raise the CO_2 tension of the latter before the subject takes the second and final breath of the experiment.

RESULTS

In table 1 we present the results of a series of 54 experiments, carried out over several days, on a subject with an average respiratory rate of 8 per minute. In each experiment the concentration of the inspired CO_2 was adjusted so as to be within a small range of the expected venous level, and the alveolar sample was taken at the end of the second expiration. It will be seen that the variation in alveolar CO_2 on each day was small, and that the values obtained were scarcely affected by the CO_2 concentration of the inspired air, though there is evidence that the alveolar CO_2 increases slightly as the concentration of the inspired CO_2 is raised.

An especially important feature is the low variation obtained in the alveolar CO_2 tension when repeated estimations are carried out with the same inspired mixture. This variation is no greater than that obtained when the subject is breathing room air.

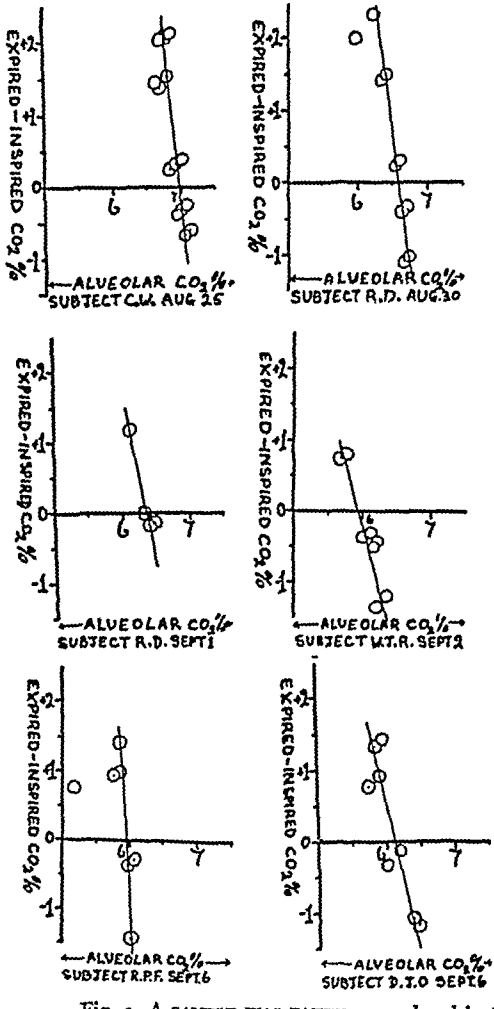

Fig. 2. A SAMPLE WAS TAKEN on each subject at the end of the second normal breath of a known mixture of CO_2 and oxygen. This was repeated two or three times with the same mixture, and then repeated with increasing concentrations of CO_2. The circles at the upper end of the line represent the lower concentrations of inspired gas, which are given in table 2.

Table 2 shows the results obtained when a larger range of inspired concentrations was used, and from these results we have calculated the CO_2 tension of the venous alveolar air in a series of five healthy subjects. In routine estimations it would not be necessary to use as many inspired mix-

TABLE 1. A SERIES OF 54 SEPARATE EXPERIMENTS ON SUBJECT C.W. INSPIRING CO_2 CONCENTRATIONS IN A SMALL RANGE CLOSE TO THE EXPECTED VENOUS LEVEL. SUBJECT BASAL. EXPIRED SAMPLE TAKEN AT THE END OF TWO NORMAL BREATHS

DATE	EXPERIMENT	INSPIRED CO_2	ALVEOLAR[1] CO_2	MEAN ALVEOLAR CO_2	
		%	%	%	*mm. Hg*
Aug. 18	1	4.97	6.62	6.50	46.1
	2	4.97	6.51		
	3	4.97	6.49		
	4	4.97	6.49		
	5	4.97	6.43		
	6	4.97	6.47		
Aug. 22	1	5.96	6.80	6.79	48.9
	2	5.96	6.82		
	3	5.96	6.76		
Aug. 22	1	6.31	6.78	6.80	49.0
	2	6.31	6.83		
	3	6.31	6.80		
Aug. 12	1	6.35	6.68	6.71	48.0
	2	6.35	6.82		
	3	6.35	6.59		
	4	6.35	6.84		
	5	6.35	6.85		
	6	6.35	6.51		
Aug. 16	1	6.35	6.63	6.73	48.6
	2	6.35	6.77		
	3	6.35	6.83		
	4	6.35	6.71		
	5	6.35	6.74		
	6	6.35	6.74		
	7	6.35	6.73		
Aug. 17	1	6.35	6.78	6.71	48.4
	2	6.35	6.72		
	3	6.35	6.70		
	4	6.35	6.68		
	5	6.35	6.67		
	6	6.35	6.65		
	7	6.35	6.72		
Aug. 18	1	6.35	6.84	6.81	48.4
	2	6.35	6.88		
	3	6.35	6.83		
	4	6.35	6.70		
Aug. 19	1	6.35	6.72	6.70	47.6
	2	6.35	6.69		
	3	6.35	6.69		
	4	6.35	6.70		
Aug. 19	1	6.44	6.98	6.91	49.1
	2	6.44	6.97		
	3	6.44	6.90		
	4	6.44	6.81		

TABLE 1.—*Continued*

DATE	EXPERIMENT	INSPIRED CO_2	ALVEOLAR[1] CO_2	MEAN ALVEOLAR CO_2	
		%	%	%	*mm. Hg*
Aug. 23	1	6.44	6.84	6.84	49.4
	2	6.44	6.94		
	3	6.44	6.84		
	4	6.44	6.75		
Aug. 23	1	6.70	6.81	6.83	49.2
	2	6.70	6.83		
	3	6.70	6.94		
	4	6.70	6.75		
Aug. 23	1	6.70	6.79	6.80	49.2
	2	6.70	6.86		

[1] These samples are termed 'alveolar' samples even though the subject is breathing CO_2 mixtures, and not room air.

tures as were employed in these experiments. The alveolar CO_2 percentages recorded in the table are means of either two or three estimations.

As already indicated the required venous value can be obtained by finding the value of CO_2 tension of the inhaled gas at which the difference (*CO_2 tension of inhaled gas* − *CO_2 tension of alveolar air*) would be zero. There is, however, a simpler practical method of deriving the result.

If there is a linear relationship between the difference (*CO_2 tension of alveolar air* − *CO_2 tension of inspired gas*) and (*CO_2 tension of inspired gas*), there is necessarily also a linear relationship between the same difference and (*CO_2 tension of alveolar air*). The two lines plotted on the same diagram would have different slopes but would cross the x-axis at the same point, for if:

Ic = the CO_2 tension (corrected for absorption of oxygen) of the inhaled gas, and

Av = the CO_2 tension of the alveolar air, then if

$$Av\text{-}Ic = mIc + K \quad \ldots\ldots\ldots\ldots\ldots\ldots (1)$$

where m and K are constants then $Av\text{-}Ic + m\,(Av\text{-}Ic) = mIc + K + m\,(Av\text{-}Ic)$ or $(1 + m)\,(Av\text{-}Ic) = mAv + K$ or

$$Av - Ic = \frac{m}{1+m}\,Av + \frac{K}{1+m} \quad \ldots\ldots\ldots (2)$$

Result 2 shows that there is a linear relationship between $(Av\text{-}Ic)$ and Av. The slope $\frac{m}{1+m}$ is different from that of *line 1* but the two lines each cross the x-axis at the point where the abscissa is $-\frac{K}{m}$. This result is of interest, because when one sets out in adjacent columns the corresponding values for $(Av\text{-}Ic)$ and Av the range in Av is seen to be very small, and it is easy to select with accuracy the value of Av which corresponds to zero value of $(Av\text{-}Ic)$.

TABLE 2.

SUBJECT	DATE	RESP. RATE/MIN.	ARTERIAL ALVEOLAR AIR CO_2[1]	INSPIRED CO_2 IC	ALVEOLAR CO_2 AV I	DIFFERENCE IC-AV	'VIRTUAL' VENOUS ALVEOLAR AIR CO_2
			%	%	%		%
C.W. (basal)	Aug. 25	8	5.80	4.60	6.68	+2.08	6.97
				5.20	6.66	+1.46	
				6.60	6.92	+0.32 ←	
				7.32	6.99	−0.33	
				7.70	7.07	−0.63	
R.D. (non-basal)	Aug. 28	20		4.36	6.39	+2.03	6.41
				4.97	6.31	+1.34	
				6.35	6.42	+0.07 ←	
				6.74	6.36	−0.38	
				7.00	6.63	−0.37	
R.D. (basal)	Aug. 30	16	5.60	4.03	6.16	+2.13	6.62
				4.97	6.41	+1.34	
				6.35	6.59	+0.24 ←	
				7.03	6.65	−0.38	
				7.79	6.72	−1.07	
R.D. (non-basal)	Sept. 1	16	5.54	4.97	6.14	+1.17 ←	6.30
				6.35	6.33	−0.03	
				6.56	6.41	−0.15	
R.D. (non-basal)	Sept. 1	26	5.80	4.42	6.51	+2.09	6.65
				4.97	6.43	+1.46	
				6.35	6.55	+0.20	
				6.56	6.66	+0.10 ←	
				7.46	6.63	−0.83	
W.J.R. (basal)	Sept. 2	9	4.90	4.97	5.72	+0.75 ←	5.90
				6.35	6.01	−0.34	
				6.65	6.18	−0.47	
				7.55	6.99	−0.56	
D.J.O. (basal)	Sept. 6	14	4.92	4.42	5.80	+1.38	6.20
				4.97	5.81	+0.84 ←	
				6.35	6.11	−0.24	
				7.55	6.41	−1.14	
R.P.F. (basal)	Sept. 6	24	5.13	4.42	5.50	+1.08	5.90
				4.97	5.81	+0.84 ←	
				6.35	6.02	−0.33	
				7.50	6.05	−1.45	

[1] Each value represents the mean of two or three separate determinations. ← Indicates the range within which equilibrium has occurred.

In table 2 we have included the venous values obtained by simple inspection and interpolation of the tabulated analysis of alveolar CO_2. In figure 2 is

shown the alternative method of deriving the result graphically in a random selection of 6 of the experiments.

DISCUSSION

Gladstone (3) pointed out the importance of the deadspace in his estimations of the mixed venous blood, and regarded it as the only obstacle to rapid mixing. He believed the lungs to be fully ventilated within 10 to 12 seconds, and stressed the importance of completing the equilibration procedure during that time owing to the danger of recirculation. The present authors agree with this reasoning and in developing their technique have found that the use of oral suction gives a satisfactory clearance of the deadspace, and enables the procedure to be completed within 10 to 15 seconds.

Recently Gray, Bing, and Vandam (4) have summarized the necessary qualities for an equilibration procedure in the light of their own experience. They say that the procedure should be simple enough for young subjects, and should be completed before recirculation of CO_2 begins. They point out that the presence of cardiac septal defects increases the possibility of early recirculation, and that therefore the pulmonary blood must be oxygenated so that constant 'virtual' values are obtained; the procedure must allow of adequate 'mixing' during the short time available; and finally, the procedure itself must not be a cause of changes in the cardiac output.

Since the composition of the blood returning to the right side of the heart is subject to the influence of a wide range of arterio-venous differences in the blood returning from the various organs, a sudden alteration in the relative amounts entering from the superior and inferior vena cava would almost certainly affect the composition of the mixed venous blood. For this reason any form of cooperation from the subject is to be discouraged, and only the normal respiratory movements of the subject should be used for introducing the CO_2 mixture. The technique must be such that the required values can be obtained within two respirations on a slow-breathing subject.

The method we have described fulfils these conditions, and we are applying it to an investigation of cardiac output, which will form the subject of a separate communication. Since no cooperation is required the technique is suitable for use on animals. For clinical cases of unknown acid-base balance and unknown A-V difference (e.g. in congenital heart disease), a suggested routine would be:—Subject basal, and recumbent for thirty minutes before the procedure. *1*) Three alveolar air samples. *2*) Six per cent CO_2 in oxygen inhaled, sample taken at the end of the second expiration. Repeat. *3*) Repeat with 6.5 per cent CO_2. *4*) Repeat with 7 per cent CO_2. (These inspired mixtures need only be approximate, so long as their composition is known).

This takes a total of about 25 minutes, and involves nine samples for analysis. Two minutes pause should be allowed between each sample. CO_2

output is measured by collecting expired air in a spirometer and analyzing the contents for CO_2.

SUMMARY

A technique for sampling alveolar air, developed in a previous communication, has been applied to the determination of venous alveolar air. This presents a means of determining cardiac output indirectly by applying the Fick principle, which accords with the requirements of a method suitable for use on inexperienced and uncooperative subjects, and experimental animals.

We are indebted to Dr. H. C. Bazett for his interest and critical advice during the course of this investigation, which was carried out with the aid of a grant from the American Heart Association.

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Studies on Acid-Base Balance Before and During Repeated Exposure to Altitude, or to Hypoxia and Hyperventilation[1]

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IN CONJUNCTION WITH SOME STUDIES of the effect of exposure to high altitude on the metabolism of ascorbic acid, it was felt advisable to study possible changes in the acid-base balance of the body. This seemed nesessary in view of the work of Hawley (1) who has shown the dependence of ascorbic acid excretion on the *p*H and alkaline reserve of the blood.

J. B. S. Haldane (2) and others have shown, as early as 1918, that when an individual is subjected to low pressure or hypoxia the urinary excretion of ammonia is greatly decreased. Sundstroem (3) in his studies on himself on the high level plateaus of southwestern United States and upon Pike's Peak, observed at first a decrease in the production of NH_3 and then on Pike's Peak a considerable temporary increase, due "to the failure of the kidneys to excrete the fixed alkalies to a sufficient extent."

There has been, at least up until 10 years ago, considerable disagreement among various investigators as to whether the acidotic effect which is observed in terminal asphyxia, is present in compensated anoxia and not in evidence due to acapnia and resultant alkalosis of hyperventilation.

Renal salt loss may be due, not only to the relative alkalosis of acapnia (4), but also to previous loss of body water (5) which has been demonstrated in rats (6). Water intake and salt intake were not controlled during this study so an increase in salt output may not be correlated with a loss of body fluid or salt. Sundstroem (3) found also that during the first few days of his exposure to high altitudes the body retained phosphorus, i.e. he had a positive phosphorus balance. As he became acclimated, however, this changed to a negative balance.

In 1920, Haggard and Henderson (7) coined the expression 'respiratory X' by which they designated the substance which stimulates the respiratory

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center in anoxia. At that time they and others emphasized the fact that after exposure to anoxia and the development of the acapnia and alkalosis, the kidney restores the H_2CO_3:$NaHCO_3$ ratio of blood by excretion of $NaHCO_3$ (or other Na salts). Then upon returning to normal O_2 tension of the air, respiration is depressed, and acidosis, as defined by the high H_2CO_3:$NaHCO_3$ ratio, occurs.

PROCEDURE

Investigations were made on two groups of subjects.

Group I. This group consisted of 11 male medical students, ages 20 to 26. These men were placed on a hospital diet, consisting of 3 different menus, occurring in sequence. These diets were controlled in all respects except the intake of water and salt. Control observations were made on the group between

TABLE 1. GROUPS I AND II, CONTROL AND EXPOSURE PERIODS

PERIOD	DATE STARTED	DATE ENDED
Group I		
1st Control	8/ 3/42	8/28/42
2nd Control	9/14/42	9/27/42
Exposure to 18,000 ft., no oxygen	9/28/42	11/29/42
Exposure to 18,000 ft. with oxygen	11/30/42	12/ 7/42
Post-exposure control period	12/ 8/42	12/17/42
Group II		
Pre-exposure control	1/18/43	1/29/43
Hyperventilation	1/30/43	2/10/43
Exposure to 35,000 ft. with oxygen	2/15/43	3/13/43
Post-exposure control period	3/13/43	3/19/43

August 3 and August 28, 1942. This constituted the first control period. After 2 weeks' vacation the group was returned to the hospital diet and observations made between September 14 and September 27, 1942. This constitutes the second control period. On September 28th, exposure to a simulated altitude of 18,000 ft. without oxygen was started. These exposures were made 3 times weekly. The ascents required about 45 minutes which included a 'level-off' period at 10,000 ft. After being at 18,000 ft. for about 60 minutes, the descent was made in approximately ½ hour. On November 29, the last ascent without oxygen was made. On and after November 30 the ascents were made to 18,000 ft. with oxygen supplied. On December 7, the last ascent with oxygen was made. Observations were continued from December 8, 1942, to December 17, 1942, and these constitute the post-exposure control period.

Group II. This group consisted of 7 male medical students, ages 20 to 25. These men were placed on the same diet, except that it contained 141 instead of 91 mg. of ascorbic acid. Their diet was controlled except for the consump-

tion of water and salt. Control observations were made on this group between January 18 and January 29, 1943. This constitutes the pre-exposure control period. On January 30, February 1, 4, 8 and 10 the group was subjected to vigorous hyperventilation for a period of one hour. The rate of breathing was paced by a metronome at 40 respirations per minute, with maximum volume exchange. Occasional rest periods of 1 or 2 minutes were permitted when signs of tetany appeared. This period from January 30 to February 10 constitutes the hyperventilation period. On February 15 ascents to 35,000 ft. with oxygen supplied by face masks from take-off to landing were instituted. The time spent at 35,000 ft. varied from one minute to 70 minutes. This variation in exposure was due to occasional occurrence of 'bends.' These exposures were continued 3 times weekly with one omission until the last ascent on March 13. From March 13 to March 19, observations were continued, constituting the post-exposure control period.

The first group was subjected to a simulated altitude of 18,000 ft., which corresponds closely to 10.5 per cent O_2. The second group was taken to a simulated altitude of 35,000 ft. but supplied pure O_2 by B.L.B. masks. These conditions give by calculation, using 47 mm. as vapor tension of water and 39 mm. as the partial pressure of CO_2 in the alveoli, an alveolar concentration of 9.7 per cent O_2 at 18,000 ft. Using 47 mm. Hg water vapor pressure and 28 mm. as the partial pressure of CO_2 in the alveoli at this altitude gives 13.5 per cent O_2 in the alveoli at 35,000 ft. with O_2 masks. At sea level the O_2 in the alveoli is 14.5 per cent (8). These calculated values ignore the factor of the actual extent of alveolar and inspirational air mixing. Assuming the values for vapor pressure of water and partial pressure of CO_2 as given, the calculated alveolar O_2 concentration is maximal. Thus even at 35,000 ft. with pure O_2 there is some anoxia. The production of an anoxemia will depend upon the individual resistance, volume exchange, etc., and occurs as indicated by the oximeter in some of our subjects.

METHODS

Analyses of the 24-hour collections of urine were made for total fixed base (Na, K, Ca, Mg), ammonia and phosphate. The total fixed base was determined by the method of Stadie and Ross (9), slightly modified.

Urine ammonia was determined by the method of Sergeev (10). Preliminary tests indicated the reliability of this method from the viewpoint of recovery of added ammonium salt. Later, upon more extended use, it was found to be unreliable for absolute amounts of ammonia in the urine. The method involves nesslerization and contrary to the claims of the author there is a considerable amount of non-ammonia chromogenic material in urine. This will be discussed later with reference to the results obtained. Urine phosphate was determined by the method of Youngberg (11) modified for the photelometer. This deter-

mination was added to the proposed list because of an increased ferric phosphate precipitate during the removal of phosphate as required by the method for total fixed base.

Determinations of urinary ketone bodies were made and routinely the $FeCl_3$ test for acetoacetic acid was used.

Often, in *Group I* especially, a positive test was obtained. These urines were then analyzed for ketone bodies. At no time, however, was an increased excretion noted. After several urines had been analyzed with negative results, the cause of the positive $FeCl_3$ test was found to be the unreported ingestion of salicylates to alleviate headache on the part of several of the subjects. When this practice ceased, the positive $FeCl_3$ tests were not found.

TABLE 2. RESULTS OBTAINED ON GROUP I, TWO CONTROL PERIODS AND NINE WEEKS OF EXPOSURE

	DATE STARTED (1942)	DATE ENDED (1942)	A TOTAL FIXED BASE	B AMMONIA	C PHOSPHATE	D VOL. URINE
Control I	8/3	8/28	2378	368		1547
Control II	9/14	9/27	2654	507	1.08	1547
Exposure week 1	9/28	10/4	2242	508	0.96	1487
2	10/5	10/11	2474	290	1.08	1531
3	10/12	10/18	2318	471	1.03	1575
4	10/19	10/25	2638	536	1.04	1574
5	10/26	11/1	2429	642	1.04	1427
6	11/2	11/8	2589	623	1.24	1543
7	11/9	11/15	2692	668	1.10	1457
8	11/16	11/22	2649	657	1.10	1513
9	11/23	11/26	2837			1534

Note: Total fixed base is expressed in cc. of 10th normal base/24 hours. Ammonia is expressed in cc. of 10th normal base/24 hours. Phosphate is expressed in gm. of *P* excreted/24 hours. Volume is expressed in cc. All values are averages of 11 subjects for the period indicated.

RESULTS

In reporting the results, 'significance' and kindred words are used in their statistical sense.

Table 2 summarizes the results obtained on *Group I*, 2 control periods and 9 weeks of exposure. No determinations were made during the exposures with oxygen or after cessation of exposures. It can be seen in Column A and B that the first and second control periods differ significantly in both total fixed base and ammonia. For the purposes of this investigation the second period of control is taken as a base line and significance of variation based on these values. Phosphate determination was started in the second control period. It will be seen from Column A that there is an initial decrease in total fixed base which was reversed irregularly until the fifth week of exposure. From then to

the end of the exposure period the amount of total fixed base excreted was significantly higher than the control period. From Column B, it will be seen that the amount of excretion of ammonia (Nessler reagent chromogen) is not significantly decreased in the first 3 weeks and later increased to a statistically significant degree to the end of exposure regime. From Column C, it will be noted that phosphate excretion follows the same pattern, at first a significantly decreased excretion and later, this time in the sixth week, a very sudden and marked increase in excretion. The urine volume (Column D) for twenty-four hours is not significantly altered.

Table 3 summarizes the results obtained on *Group II*. From Column A it can be seen that the amount of total fixed base excreted is markedly increased in the hyperventilation period and during the subsequent exposures to high altitude does not decrease but remains higher than during the control period and continues to increase slowly up to and after the last exposure. The ammonia excretion (Nessler's reagent chromogen), (Column B), is not altered by the hyperventilation but by continued exposure to the high altitude (1st, 2nd, 3rd week) the amount excreted is increased significantly. In the fourth and fifth weeks there is a slight drop not statistically significant. Phosphate excretion (Column C) increases markedly during the hyperventilation period, decreases in the first week of exposure and thereafter increases slowly to the end of the exposure period. There is no significant variation in the 24-hour volume of urine. Recent determinations indicate that ⅓ to ⅔ of the Nessler reagent chromogenic material in urine is not ammonia. Thus the variations which have been noted may have been in the non-ammonia fraction of the chromogenic material. Or again the variations may have been in both ammonia and the other chromogen, or in ammonia alone.

DISCUSSION

Group I. It has long been known that exposure to anoxia produces hyperventilation and resulting alkalosis. This is borne out in this investigation by the increased excretion of fixed base. This hyperventilation alkalosis is also known to decrease excretion of 'acid metabolites' such as ammonia and phosphate. This phenomenon is noted in this investigation only as a very immediate effect. Later in the period of exposure the acid metabolites are increased. This would seem to indicate an acidotic condition, at least metabolically.

Group II. This group was subjected to a series of hyperventilation periods before the exposures to 35,000 ft. were initiated. In this series of hyperventilation periods the increased total fixed base excretion is paralleled by the increased excretion of acid metabolites. These values, of course, are on the 24-hour excretion. Thus any immediate effect may be marked by a later compensatory effect in the opposite direction. In *Group II* there is no immediate

decrease in the values of total fixed base and phosphate such as was noticed in *Group I*. This may be due to the conditioning received in the hyperventilation periods.

The explanation for the seeming conflict between the excretion of an increased amount of total fixed base and also of the acid metabolites, ammonia and phosphate lies, quite probably, in the fact that during hypoxia, the hyperventilation produces a primary CO_2 deficit and a relative alkalosis. Upon restoration of the normal oxygen tension the 'rebound' acidosis due to decrease in rate of respiration stimulates the production of acid metabolites, ammonia and phosphate buffer.

McCance (12), in reporting experimental human salt deficiency, included some experiments in hyperventilation which are interesting. He reported no change in phosphate excretion. This, however, was on the immediate samples of urine, not 24-hour specimens. The rebound acidosis might well bring the

TABLE 3. RESULTS OBTAINED ON GROUP II

PERIOD	DATE STARTED (1943)	DATE ENDED (1943)	A TOTAL FIXED BASE	B AMMONIA	C PHOSPHATE	D VOL. URINE
Control	1/18	1/26	2343	550	1.03	1154
Hyperventilation	2/5	2/11	2885	552	1.29	1263
Exposure week 1	2/14	2/20	2931	624	1.17	1324
2	2/21	2/27	2871	717	1.20	1413
3	2/28	3/6	2994	647	1.19	1393
4	3/7	3/13	3150	585	1.23	1353
5	3/13	3/19	3414	604	1.26	1334

Note: Total fixed base is expressed in cc. of 10th normal base/24 hours. Ammonia is expressed in cc. of 10th normal base/24 hours. Phosphate is expressed in gm. of *P* excreted/24 hours. Volume is expressed in cc. All values are averages of 7 subjects for the period indicated.

phosphate excretion above normal. This, however, needs further study which might be done by analyzing hour by hour samples of urine in a few cases of exposure to 18,000 ft.; 35,000 ft. with O_2 and hyperventilation. Data collected on this point on hyperventilation studies on 2 subjects tend to confirm the rebound acidosis hypothesis.

SUMMARY

The 24-hour urines of groups of male medical students have been analyzed before and during exposure to high altitude at 18,000 ft. without O_2, to hyperventilation and to high altitude at 35,000 ft. with O_2. Excretion of total fixed base, after an initial decrease, increases with repeated exposure to 18,000 ft. Excretion of total fixed base increases as a result of hyperventilation. Excretion of total fixed base increases as a result of exposure to 35,000 ft. with oxy-

gen. Excretion of acid metabolites, ammonia and phosphate parallels the excretion of total fixed base in all cases. There is no significant variation in the 24-hour urine volume. The data indicate that a rebound acidosis follows the period of acapnic alkalosis and that there is a continuous increase in the excretion of fixed base as well as in that of the acid metabolites.

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Effect of Repeated Exposure of Human Subjects to Hypoxia on Glucose Tolerance, Excretion of Ascorbic Acid, and Phenylalanine Tolerance[1]

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SINCE CARBOHYDRATE METABOLISM is closely related to oxidative mechanisms and is easily followed by comparatively simple methods, the glucose tolerance of subjects exposed repeatedly to hypoxia was investigated. Leipert and Kellersman (1) have reported that glucose tolerance at low pressure (simulated 18,000-ft. altitude) is decreased in the hypoglycemic phase. They interpret this as a tendency toward decreased assimilation of glucose by the tissues. We have attempted to confirm their observations.

Considerable variation in the excretion of ascorbic acid in subjects exposed to hypoxia at low pressure has been reported by Krasno *et al.* (2) and confirmed later both in this laboratory and elsewhere. The ascorbic acid phase of this study is primarily an extension of these previous reports.

An increased excretion of substances reacting with 2,4-dinitro-phenylhydrazine (keto-substances) was observed in this laboratory in a few subjects repeatedly exposed to 18,000 ft. without supplemental oxygen (3). Sealock and Silberstein (4) have extensively investigated the relation of ascorbic acid to the metabolism of the aromatic amino-acids. Since an anomaly in ascorbic acid has been observed in a few subjects after repeated exposure to hypoxia, it seemed advisable to investigate the excretion of keto-substances of our subjects with oral administration of an aromatic amino-acid phenylalanine.

PROCEDURE

Six human, male subjects, ages 20 to 27 years, maintained on a fixed diet controlled as to the fat, carbohydrate and protein content, as well as vitamin, mineral and water intake, were used. These subjects were maintained on this diet, without exposure to hypoxia for a period of 4 weeks, after which they were exposed 3 times weekly for 1.5 hours to a simulated altitude of 18,000 ft.

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without oxygen inhalation in a decompression chamber. Toward the end of the exposure period, which lasted 7 weeks, they were exposed 6 times weekly for 3 weeks. Ground level observations and determinations were made twice on glucose tolerance, ascorbic acid excretion and phenylalanine tolerance during the control period. During the exposure period, glucose tolerance was determined weekly, a total of 7 times, the ascorbic acid excretion twice and hourly for 24 hours, and the phenylalanine tolerance 3 times. No observations were made during the post-exposure period. Exposure to low pressure was made each time at least 2.5 hours after the preceding meal.

METHODS

Glucose Tolerance. Seventy five gm. of glucose in 500 cc. of water were given to each subject 30 minutes before the exposure period was initiated.

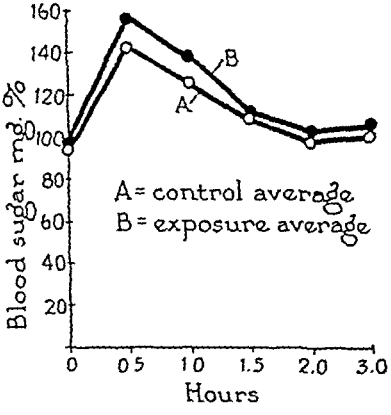

FIG. 1. GLUCOSE TOLERANCE of control and exposure groups.

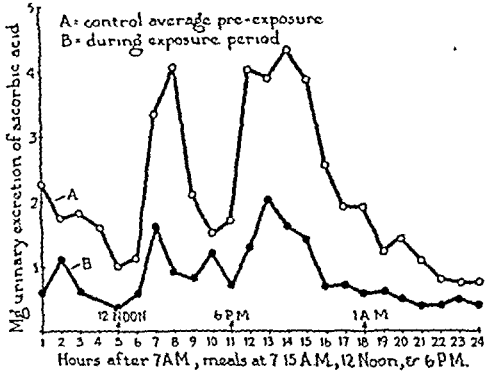

FIG. 2. ASCORBIC ACID EXCRETION during control and exposure periods.

The control tests were made under similar conditions without exposure. Finger blood glucose was determined at 0, 0.5, 1, 1.5, 2 and 5 hours after ingestion of the glucose. Glucose was determined by the method of Hagedorn and Jensen (5).

Ascorbic Acid Excretion. Excretions were determined on hourly samples of urine collected during a 24-hour period. The sum of these excretions is the total daily excretion.

Phenylalanine Tolerance. Four grams of D,L-phenylalanine were given orally in suspension in water or tea about 30 minutes before commencing the ascent in the decompression chamber. This dosage had been previously found to give a moderate increase in excretion of keto-substances (substances reacting with 2,4-dinitro-phenylhydrazine), the increase being due, at least in part, to phenylpyruvic acid and p-hydroxy-phenylpyruvic acid. This was determined by isolation of the acids and determination of their melting points

and of the purified hydrazones by Dr. Theodore Friedemann. The excretion was determined on hourly samples for 14 hours, beginning 2 hours preceding and for 12 hours following ingestion of the phenylalanine, using the method of Penrose and Quastel (7), adapted by use to the Evelyn photoelectric colorimeter. The test dose was given at the same time of day during the pre-exposure and the exposure period, and one hour before ascent in the altitude chamber.

RESULTS

Glucose Tolerance. The averaged results (4 control and 6 exposure tests) are shown in figure 1. They fail to reveal a significant variation in the response observed during the exposure period as compared to the control period. The blood sugar values, however, are consistently higher during the exposure tests.

TABLE 1. DATA SHOWING THAT 4 GM. OF PHENYLALANINE GIVEN ORALLY INCREASES THE URINARY OUTPUT OF SUBSTANCES REACTING TO 2,4-DINITROPHENYLHYDRAZINE

SUBJECTS	NO. TESTS	OUTPUT OF KETO-SUBSTANCES				
		Control		24-hour excretion after 4 gm. phenylalanine		
		Av.	Range	Tests 1	2	3
		mg.	*mg.*	*mg.*		
Do	11	119	59–161	256	187	272
Ho	11	131	111–161	260	225	209
Mi	13	86	72–106	373	329	309
Mo	13	129	88–165	305	339	346

Ascorbic Acid Excretion. In figure 2, the averaged results obtained from assaying the hourly output of ascorbic acid in the urine of the subjects for 24 hours is graphed. *Curve A* represents the results during the control or pre-exposure period. The average excretion during this period was approximately 49 mg. *Curve B* represents the results during the last 2 weeks of the exposure period. The average excretion during this period was approximately 20 mg.

Similar results were recorded in the group of subjects exposed to 18,000 ft. and on the same intake of ascorbic acid, 91 mg. (8).

Phenylalanine Tolerance. To determine the dose of phenylalanine that would result in a slight but definite increase in the output of keto-substances, 4 subjects kept on a constant diet were used. They were different subjects from those being used in the present anoxia study. The output was determined on control days and after the administration of 1 and 2 gm. of phenylalanine and after the administration of 4 gm. The 4-gm. dose was the amount found to give an increased urinary output of keto-substances. This is illustrated by the data in table 1.

Data obtained by giving 4 grams of phenylalanine to the subjects during the pre-exposure and exposure period are shown in table 2. It is clear that the repeated exposure to anoxia did not affect the phenylalanine tolerance in these subjects, even though the output of ascorbic acid in the urine averaged approximately 20 mg. daily at the time.

DISCUSSION

The results of the glucose tolerance tests indicate that there was no decided change in the ability of the tissues to assimilate glucose under these conditions of hypoxia at low pressure. Thus we were not able to confirm the observations of Leipert and Kellersman, that a decrease in the oxygen tension abolished or minimized the hypoglycemic phase of the tolerance curve. In

TABLE 2. EXCRETION OF PHENYLPYRUVIC[1] DURING 14 HOURS AFTER TEST DOSE OF 4 GM.

SUBJECT	CONTROL TEST		TEST DURING PERIOD OF EXPOSURE		
	A	B	C	D	E
1	202	187	207	207	159
2	154		122	140	121
3	198	165	203	206	196
4	165	114	183	110	147
5	237	260	274	304	249
6	176	154	188	134	147
Av. excretion for group	181		183		

[1] The figures refer to the total excretion of substances reacting with 2,4-dinitrophenylhydrazine, expressed as milligrams of phenylpyruvic acid, during 2 hours before and 14 hours after administration of 4 gm. of phenylalanine.

fact, on the average our group of subjects manifested no hypoglycemic response to the test dose. They may have been due to the difference in length of exposure, and to the fact that these German subjects were under considerable psychic stress (such as writing tests) which was absent under our conditions.

Ascorbic acid excretion, when the daily intake is 91 mg., is decreased by repeated exposure to hypoxia. This is most likely due to an increased utilization of the vitamin as a result of exposure to hypoxia. The decreased excretion of ascorbic acid was not confined to the period of relative hypoxia, but, as the graphs of hourly excretion show (fig. 2), was low throughout the 24-hour period.

The tolerance to phenylalanine was not changed under the experimental conditions to which these subjects were exposed. The few subjects who in a previous study by Krasno showed a hydroxyphenylketonuria, a finding which prompted this study, were medical students who were under the stress of examinations in school as well as strenuous tests in the altitude chamber.

CONCLUSIONS

Glucose tolerance was not decidedly changed in 6 subjects when exposed to 18,000 ft. without supplemental oxygen for 1.5 hours. The excretion of ascorbic acid was markedly decreased by repeatedly exposing the subjects to 18,000 ft. without benefit of supplemental oxygen when the daily intake of the vitamin was 91 mg. Phenylalanine tolerance was not affected by exposure to 18,000 ft. without the benefit of supplemental oxygen.

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Effect of Physical Training on Capacity to do Work as Measured by the Bicycle Ergometer

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THE FIRST SCIENTIFIC APPROACH to the measurement of work output in man is reputed to have been made by Lavoisier in 1770. He accomplished the measurement of work by having subjects sit in a chair and rotate a pedal attached to their right foot. Thus, Lavoisier deserves the credit for devising the first bicycle ergometer. In 1898 Zuntz (1) published the first report in which a bicycle ergometer was used as an instrument for measuring work. In this country Atwater (2) in 1889 was the first to report experiments in which the bicycle ergometer was used to measure work in man. From this time on, the types of bicycle ergometers as well as their applications to the problems of work have been many and varied. The modern type of bicycle ergometer was described by Kelso and Hellebrandt (3). This later type, with some modifications as described by Tuttle and Wendler (4), is used for obtaining the data in the experiment reported at this time.

Measurement of Work Capacity. The first problem to be settled in measuring capacity to do work is the adoption of some criterion of work capacity. Hellebrandt *et al.* (5) practiced having subjects ride a bicycle ergometer to exhaustion, the endpoint for exhaustion being the inability to maintain a predetermined rate of working. The predetermined work rate varied from 0.29 to 0.39 H.P. Hellebrandt, using women for subjects, found this to be a rather heavy work rate since they exhibited the exhaustive reaction in less than one minute. The time interval that the predetermined work rate was maintained was used as the criterion of work capacity. The rate of working was recorded in terms of volts. By referring to the voltage record the appearance of the exhaustive reaction was graphically obtained.

Karpovich and Pestricov (6) made use of a friction brake type bicycle ergometer. Their criterion of work capacity was similar to that of Hellebrandt. However, since their ergometer was not equipped with a recording voltmeter they resorted to pedaling rate as a criterion, but expressed the work capacity in foot pounds as well as time. Work capacity was regarded as the amount of work accomplished from the beginning of the bout until the subject was unable to maintain the predetermined work rate. In one experiment the pre-

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determined work rate varied from 0.159 to 0.261 H.P. and required 60 to 70 pedal revolutions per minute. After considerable practice one subject was able to maintain a work rate of 0.217 H.P. for 6 minutes, 12 seconds. In another experiment, the predetermined work rate was 0.506 H.P. and required 117 pedal revolutions per minute. The maximum time this rate of working was maintained was 6 minutes, 18 seconds.

METHODS AND RESULTS

The procedure used for obtaining the data in the experiment reported here, relative to capacity to do work is as follows: Sufficient resistance is put into the generator field of the bicycle ergometer, so that when the pedals are turned at a rate of 60 rpm the work rate is 0.33 H.P. The subjects pedal against this resistance as fast as they can for a predetermined time, either one or two minutes. The output of the generator is recorded in volts. Since the recording paper is pulled past the recording pen by a synchronous motor, additional timing devices are not required. The speed of the recording paper is such that

TABLE 1

CLASSIFICATION	NUMBER SUBJECTS	MEAN HEIGHT in.	MEAN WEIGHT lb.	MEAN SURFACE AREA m^2
P. E. majors	34	64.5	129	1.62
Student nurses	65	64.3	128	1.61
Random sampling	73	64.5	127	1.61

the vertical lines set off 15-second intervals. A typical record is shown in figure 1.

The procedure for calculating the work accomplished is as follows: five-second intervals are marked off on the work record with the use of a stencil designed especially for this purpose. The mean height of the curve for each 5-second interval is determined by inspection. The voltage equivalent of each point thus determined is found by counting the number of horizontal lines between the point and the base-line, and multiplying them by 0.2 which is the calibrated voltage equivalent of each horizontal line. The mean voltage generated per minute is found by calculating the average of 12 points established as described above. The work accomplished during the minute in question is found in kilogram meters per minute by referring to a conversion table constructed for this purpose. Maximum work rate is found by determining the highest point on the work curve in terms of volts generated, and then expressing this value in terms of kilogram meters by referring to the conversion table mentioned previously.

Work Capacity Classification. In order to test the procedures and assumptions as to the reliability of the bicycle ergometer as an instrument for classifying people as to their work capacity, the experiment described subsequently

ras carried out. One hundred seventy-two female subjects, ranging in age rom 18 to 25 years, including physical education majors, student nurses and . random selection of undergraduate students, were studied. Investigation howed that the physical education majors participated in a program of ystematic and rather strenuous physical activity. The nature of the work f the students of nursing kept them rather closely confined, and prevented hem from participating in any regular program of systematic physical training. Also, during the period of this experiment severe physical demands were eing made on student nurses, the nature of which appeared to detract from a eak condition of work efficiency. We attempted to get no information relative o the physical condition of the random sampling of subjects except that hey were not participating in any systematic program of conditioning exer-

TABLE 2. SUMMARY OF THE MEAN WORK CAPACITY OF PHYSICAL EDUCATION MAJORS, SUBJECTS PICKED AT RANDOM AND STUDENT NURSES

	MEAN	S.D.	SIGMA OF MEAN
	kg. m/min.		
1st min. work			
P. E. majors	2117.7	265.9	45.60
Random sampling	1781.5	297.4	34.81
Student nurses	1612.5	205.8	25.53
2nd min. work			
P. E. majors	1183.8	235.9	40.47
Random sampling	966.1	221.1	25.99
Student nurses	820.4	137.5	17.05
Maximum work rate			
P. E. majors	3076.5	478.5	82.06
Random sampling	2617.1	577.0	67.53
Student nurses	2722.3	384.1	47.64

cises. An attempt was made to match the subjects as to surface area. The mean size of the subjects is shown in table 1.

Classified subjectively on the basis of information at hand relative to the subject groups, the physical education group should rank highest in capacity to do work, the random sampling should be second and the student nurses should have the least work capacity. In order to test our assumption, each member of the group came to the laboratory and rode the bicycle ergometer for 2 minutes at maximum effort. In this experiment the work period was extended to 2 minutes so as to obtain data relative to the nature of the work curve, and to determine if anything was gained by extending the work period from 1 minute to 2 minutes. A summary of the data is given in table 2.

The data in table 3 show that the physical education majors have a significantly greater work capacity than either the subjects picked at random or the student nurses regardless of whether work during the first minute or

work during the second minute is used as the basis of comparison. The data also show that the physical education group excels all others in maximum work rate. It is also evident from the data that the subjects picked at random surpass the student nurses in maximum work output. However, the difference in maximum work rate between the random sample and the student nurses is not highly significant.

Nature of Work Curve. The curve of work resulting from exhaustive exercise presents numerous points of interest (see fig. 1). It will be noted that it required approximately 10 seconds for the subject to acquire the maximum work rate. This point is maintained only for an instant, after which the work becomes progressively less, reaching a plateau in about 75 seconds. The plateau is maintained for the remainder of the work period. This plateau is

TABLE 3. COMPARISON OF WORK CAPACITY OF PHYSICAL EDUCATION MAJORS, SUBJECTS PICKED AT RANDOM AND STUDENT NURSES

	C.R.	LARGER MEAN
1st min. work		
P. E. majors vs. random sampling	5.86	P. E. majors
P. E. majors vs. student nurses	9.86	P. E. majors
Random sampling vs. student nurses	3.91	Random sampling
2nd min. work		
P. E. majors vs. random sampling	4.51	P. E. majors
P. E. majors vs. student nurses	8.28	P. E. majors
Random sampling vs. student nurses	4.68	Random sampling
Maximum work rate		
P. E. majors vs. random sampling	4.38	P. E. majors
P. E. majors vs. student nurses	3.73	P. E. majors
Random sampling vs. student nurses	1.27	Diff. not highly significant

designated as the fatigue level of work and is a point of differentiation between the physically trained and untrained subject. In the group of physical education majors who practiced strenuous physical training consistently, the fatigue level was evident in every case. In the group of subjects picked at random who did not participate in physical training programs, the fatigue level seldom made its appearance. The characteristic of the work curve of the untrained was a gradual decrease in work output, beginning with the maximum work rate, and continuing throughout the work period.

It was suggested that the work equivalent of the fatigue level might be highly related to work capacity. This was tested by correlating the total work accomplished for one minute with the work equivalent of the fatigue level. The coefficient for a group of 34 trained subjects was 0.821. This is evidence that the greater the work capacity under a condition of fatigue the higher the fatigue level.

It occurred to us that further information relative to work capacity might be gained by having subjects work for 2 minutes instead of one minute. A correlation of the maximum work output of all subjects used in the experiment for the first minute with that of the second gave a coefficient of 0.942. This was evidence that nothing much was gained relative to work capacity by extending the working time from one minute to 2 minutes. Besides, severe exhaustive reactions occurred in many cases as a result of a 2-minute ride at maximum effort. These included nausea, vomiting, dizziness, syncope, extreme postexercise muscle soreness, and, in addition, resentment toward the work. Since these symptoms seldom occur as a result of one-minute work at maximum effort, the amount of work accomplished in one-minute work at maximum effort is regarded as the better criterion of work capacity.

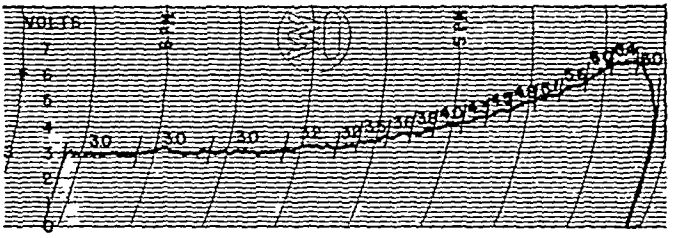

Fig. 1. RECORD OF MAXIMUM WORK OUTPUT for a period of 2 minutes expressed in terms of volts Read from right to left.

SUMMARY AND CONCLUSIONS

A method is described for measuring work and for classifying individuals on the basis of their capacity to do work, by use of the bicycle ergometer. In addition, the method of classification was applied to a group of 172 women, including physical education majors, subjects picked at random and student nurses. On the basis of the data, the following conclusions are justified:

1) The work which an individual performs in one minute of maximum effort is as good a criterion of work capacity as the amount accomplished in 2 minutes. In addition, by working only one minute severe exhaustive reactions are avoided. 2) Maximum work rate is attained in approximately 15 seconds, but is maintained for only a few seconds after which there is a gradual decline in maximum work output. In physically well trained subjects this decline continues for, on the average, 75 seconds, after which a plateau or fatigue level of work is reached and maintained for the remainder of the 2-minute work period. The height of the fatigue level of work is highly correlated with capacity to do work. 3) On the basis of data collected relative to work output, physical education majors who participated in regular bouts of strenuous exercise had a significantly greater capacity to do work than either

student nurses or subjects picked at random. Student nurses had the least capacity to do work while the subjects picked at random fell between the student nurses and the physical education majors in this respect.

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Effects of Desoxycorticosterone Acetate on Acclimatization of Men to Heat

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A DEFICIENCY OF SODIUM CHLORIDE produced by failure to replace fully that lost in the sweat increases the susceptibility of men working in the heat to heat exhaustion and results in greater elevations of body temperature and heart rate (1) These workers and Dill (2) have also found that inadequate replacement of salt lost in the sweat results in failure of men to replace fully their water losses with consequent loss of body weight. Adolph *et al.* (3) reported 'dehydration exhaustion' characterized by reduction of plasma volume and failure in temperature regulation when men working in desert heat became dehydrated. Ladell (4), Moreira *et al.* (5) and Conn *et al.* (6) have found that hormones of the adrenal cortex reduce the excretion of sodium chloride in the sweat and urine of men exposed to hot environments. Moreira *et al.* (5) found that circulatory and temperature regulatory responses to heat of fully acclimatized men on a high salt intake were not altered by intravenous injections of cortin. During the experimental period their subjects never developed salt deficits even without the aid of the injected cortin. Clinton and Thorn (7) found that administration of desoxycorticosterone acetate to men for several days increased their blood volumes during rest in a cool environment. From these reports it seemed possible that if administration of desoxycorticosterone acetate to an unacclimatized man could reduce or prevent the development of a salt deficit during the first days of work in the heat it might help to prevent the marked elevations of body temperature and heart rate so characteristic of the unacclimatized state. Consequently the present study was planned to determine the effects of desoxycorticosterone on the salt balance, temperature regulation and circulatory responses of men during acclimatization to work in a hot environment. It was not presumed that this might be a practical measure in facilitating the acclimatization of men to heat since physiological acclimatization would be necessary in any case for satisfactory life in the heat. Rather our purpose was to gain further knowledge of acclimatization and of the overall effects of the hormone in adaptations of men to heat.

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METHODS

Four normal, healthy, adult human males were used as subjects in this study. The experiments were conducted in the winter when the subjects were unacclimatized to heat. Each of the 4 subjects went through two series of work experiments beginning with 4 daily 2-hour walks on the treadmill at 5.6 km/hr. up a 2.5 per cent grade in a cool environment (21.6°C. ± 0.5° with 40% relative humidity) and continuing immediately with 5 or more days in the heat (50.5°C. ± 0.5° with 15% humidity). Subjects *R. S.* and *R. M.* were exposed to the heat 6 hours each day, walking on the treadmill during the first, fourth and sixth hours and resting during the second, third and fifth hours. Because of time limitations subjects *S. R.* and *R. K.* were exposed to the heat for only $2\frac{1}{2}$ hours a day for 5 days. *S. R.* worked for 2 hours and *R. K.* $1\frac{1}{2}$ hours during the $2\frac{1}{2}$-hour exposures. The men kept their body weights

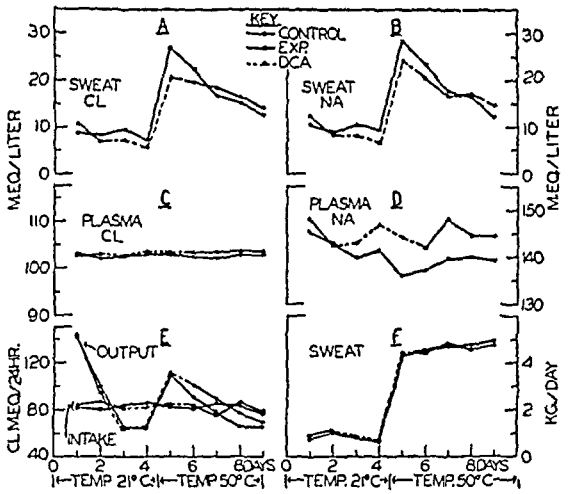

Fig. 1. MEAN VALUES OF CHLORIDE in sweat, sodium in sweat, chloride in plasma, sodium in plasma, total daily chloride exchange and daily sweat secretion of the 4 subjects in the 2 series of experiments. Broken lines indicate days of DCA administration.

constant during all experiments by drinking at frequent intervals measured quantities of water which was kept at a temperature of 36°C. They spent the remainder of the day working in a cool laboratory with unrestricted water intake. The men were on a strictly controlled daily diet containing an average of 80 mEq. of chloride and 75 mEq. of sodium throughout each series of experiments.

In one series the men received intramuscular injections of desoxycorticosterone acetate (DCA)[2] in sesame oil each morning for either 2 or 3 days before entering the heat, with a final injection on the first day in the heat. Dosages of 5 mg/day for 3 days before exposure with $2\frac{1}{2}$ mg. the first day in the heat, and 10 mg/day for 2 days before exposure with 5 mg. the first day in the heat were found to be equally effective. Injections of DCA were stopped after the first day in the heat in order to observe the disappearance of any effects it might have. The men worked in pairs, one receiving the DCA and

[2] The desoxycorticosterone acetate for this study was provided by the Schering Corporation, Bloomfield, New Jersey.

the other acting as his own control for a later series during which he received the DCA and the first man established a control. At least 5 weeks elapsed between the two series of experiments in order that the men might undergo a loss of acclimatization before starting the second series.

Measurements of the men's heart rates by a cardiotachometer, rectal temperature by clinical thermometer and skin temperature by thermocouples were made every half hour during the experiments. Oxygen intake was measured by analysis of expired air samples collected near the end of the first and last hours of work. Daily samples of urine, sweat and plasma were analyzed for sodium and chloride throughout each series. Representative samples of 24-hour urine collections were analyzed. Venous blood was drawn for plasma and hematocrit during the second hour of work. Sweat secretion was measured by weight change, taking into account evaporation from the lungs, metabolic weight loss, food and water ingested and urine voided. The sweat samples analyzed represented all of the sweat secreted during the daily experiments, the solid components being collected by carefully washing each man with 4 liters of distilled water at the end of the exposure and collecting representative samples of the wash-water. The men's clothing, exclusive of shoes, was thoroughly rinsed in the wash-water before the samples were taken. Dry heat (50.5°C. with 15% relative humidity) was used in order that the men's sweat would evaporate without loss by dripping.

Chloride in plasma and urine was determined by the Volhard titration (8). Sweat chloride was determined by the mercuric nitrate method of Schales and Schales (9). All sodium determinations were made on the Beckman flame spectrophotometer at a wave length of 595 mμ. Two standard solutions were read with each unknown, one being more concentrated and the other more dilute than the unknown. It was necessary to ash the plasma samples for analysis with the flame spectrophotometer to avoid blockage of the atomizer.

Blood volume determinations were made on the men in the cool environment before the DCA injections were begun and on the first day of exposure to heat in each series. Similar data on blood volume were secured from 4 additional subjects (*J. D.*, *R. R.*, *R. L.*, and *V. C.*), the experiments being carried out and controlled in the same manner as described for the original 4 subjects. In the experimental series these man received 10 mg. DCA per day for 3 days before entering the heat and 5 mg. on the morning of exposure. This is one day more than it was given to the other subjects on this dosage. All blood volume determinations were made during the second hour of work by injections of the blue dye T-1824 (10, 11). The plasma concentrations of the dye were determined with the Evelyn photoelectric colorimeter.

RESULTS

The administration of desoxycorticosterone acetate (DCA) to the men was accompanied by a reduction of the concentrations of sodium and chloride

in their sweat during the first 2 days of exposure to the heat (figs. 1*A* and *B*). However, the reduction in salt loss by the sweat glands with DCA was small and the urinary output was high enough that the over-all salt balance of the men was not improved. In all cases they developed a salt deficit during the first 2 days in the heat (fig. 1*E*). After the effects of the DCA had subsided during the fourth and fifth days in the heat, the men showed a continued reduction of sweat sodium and chloride, the values being about the same as corresponding values in the control experiments. In the cool environment the salt concentrations in the unacclimatized men's sweat were not significantly altered by DCA. They were very low in the cool environment as compared with values observed in the heat, even after 5 days of acclimatization to heat (figs. 1*A* and *B*). This difference is associated with differences in their skin temperatures and rates of sweating in the two environments (figs. 1*F* and 2*B*). The data in figure 1*E* show that even in the cool environment where salt loss in the sweat was only 6 to 8 mEq/day, the men excreted more salt during the

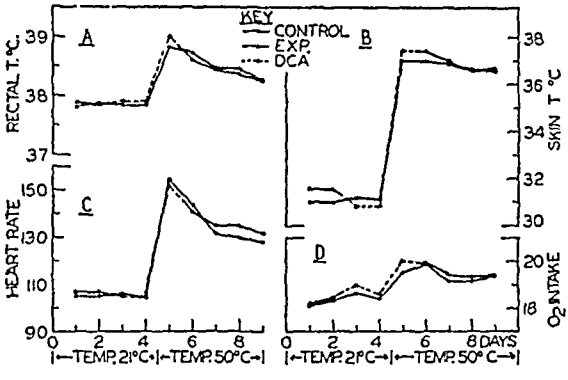

Fig. 2. MEAN VALUES OF RECTAL TEMPERATURE, skin temperature, heart rate and O_2 intake of the 4 subjects in the 2 series of experiments. The averages of heart rate, rectal temperature and O_2 intake represent values observed at the end of the hourly work periods, those of skin temperature are of measurements made after 30 and 55 minutes of each hour of work. Oxygen intake is expressed in cubic centimeters of O_2/kg. body wt/min. Broken lines indicate days of DCA administration.

first 2 days than their reduced intake (80 mEq/day). By altering kidney function they partially restored the deficits during the third and fourth days by reducing salt output below the intake but they still had small salt deficits at the time they first entered the heat.

The observed concentrations of sodium in the men's plasma were 3 to 8 mEq/l. higher on the average when DCA was administered than in the control experiments but the plasma chloride appeared to be unaffected by DCA (figs. 1*C* and *D*). The amount of sweat secreted by the men each day was not significantly altered by the administration of DCA either in the exposure to heat or when they were working in the cool environment (fig. 1*F*). In both series of experiments the stress was severe enough that the average rate of sweating of the men during the work periods increased from 1.4 to 1.6 kg/hr. from the first to the fifth days of acclimatization to heat. The course of this phase of acclimatization was not altered by DCA.

Mean values of heart rate, oxygen intake, rectal temperature and skin temperature for the 4 men during the work periods are given in figure 2. The changes of these four measurements in relation to environmental changes and

acclimatization closely parallel each other. These measurements show that the administration of DCA did not significantly improve the responses of the men to the work, either in the cool or the hot environment. The average heart rates were about the same with DCA as without it. The men were actually slightly hotter and their metabolic rates were a little higher with DCA than in the control series but these small differences are of doubtful significance statistically. Both sets of data indicate normal acclimatization of the men to work in the heat with progressive lowering of body temperature, heart rate and oxygen intake after the first exposure as previously described by Robinson *et al.* (12).

The data on the blood volumes of the working men are given in table 1. There was an increase of blood volume above the control value by every man upon the first exposure to the heat, the average increase being 11 per cent. The increments in blood volume associated with the first exposure to heat were about the same when the men had received DCA as in the experiments in which no DCA was administered. On the basis of average values the increase in blood volume on the first day of exposure to heat was brought about by increasing both plasma and cell volumes in about equal proportions. During the second to fifth days in the heat hematocrit values decreased moderately, indicating a further increase in the plasma volume (table 1). The decrease in hematocrit took place somewhat more rapidly in the series of experiments in which the men had received DCA than in the control series. Bazett *et al.* (13), Conley and Nickerson (14) and Glickman *et al.* (15) have also observed increases of plasma volume with lowered hematocrit in resting men during acclimatization to heat.

DISCUSSION

Under the conditions of these experiments the only clear-cut alterations in the responses of the subjects during acclimatization to heat which could be ascribed to the administration of DCA were higher concentrations of plasma sodium and reductions in the salt concentration in their sweat during the first 2 days of exposure. This reduction confirms in part the results of Conn *et al.* (6) Ladell (4) and Moriera *et al.* (5). Our results differ from those of Conn, however, in that after the effects of DCA had subsided on the fourth and fifth days in the heat the men showed a continued reduction of the salt in the sweat whereas Conn reported a marked rise in sweat chloride upon cessation of exogenous DCA during daily exposures of men to work in humid heat. This secondary rise indicated that the activity of the adrenal cortex had been reduced by a few days of aid from an exogenous source. Our experiments in the heat were continued for 8 days on one control subject and one who had received DCA in order to determine if the disappearance of the effects of DCA might be delayed beyond 5 days. There was still no secondary rise of sweat chloride or sodium by the experimental subject and the continued course of his acclimatization was the same as that of the control subject. This difference

between our results and Conn's is probably due to the fact that our subjects were on a relatively low salt intake (80 mEq/day) and the administration of DCA did not provide sufficient aid to prevent them from developing salt deficits due to the greatly increased sweat loss during the first days of exposure to heat (fig. 1). Therefore the salt-conserving mechanism was under stress from the beginning of the exposures to heat and this evidently stimulated the adrenal cortices to increased activity and resulted in the continued lowering of the salt concentration in the sweat. In fact adrenal activity was probably increased to some extent, even before the first exposure to the heat as the men were forced to reduce their salt output because of the deficits which they had incurred during the first 2 days on the reduced intake. The fact that on the

TABLE 1. BLOOD VOLUMES OF MEN AS AFFECTED BY WORK IN THE HEAT AND BY THE ADMINISTRATION OF DCA

SUBJ.	ROOM T. 21.6°C.			ROOM T. 50.5°C.						DAY	TEMP.	AV. 4 MEN % HEMATOCRIT	
				DCA			Control						
	Plasma Vol.	Cell Vol.	Blood Vol.	Plasma Vol.	Cell Vol.	Blood Vol.	Plasma Vol.	Cell Vol.	Blood Vol.			DCA	Control
SR	2830	2650	5480	3180	2900	6080	3230	2850	6080	1	21.6	46.1	45.7
RK	3100	2655	5755	3600	3030	6630	3320	3010	6330	2	21.6	45.9	46.7
RM	3105	2600	5705	3410	2950	6360	3460	2960	6420	3	21.6	46.9	46.9
RS	3520	2530	6050	3600	2810	6410	3510	3080	6590	4	21.6	46.5	46.1
JD	3300	2655	5955	3740	2760	6500	3700	2990	6690	5	50.5	45.9	46.8
RR	3110	2920	6030	3550	3440	6990	3480	3320	6800	6	50.5	45.4	45.9
RL	2935	2935	5870	3250	3330	6580	3200	3320	6520	7	50.5	45.2	45.8
VC	3820	3220	7040	4220	3480	7700	3890	3450	7340	8	50.5	44.6	45.5
										9	50.5	45.2	44.8
Mean....	3215	2771	5986	3569	3086	6656	3474	3123	6596				

In the heat all determinations were made during the second hour of work on the first day of exposure. In one of the series DCA was administered through the first day in the heat. Hematocrit determinations on venous blood were made daily on the first 4 of the men listed.

first day in the heat salt concentrations in their sweat were somewhat lower than values usually reported for unacclimatized men may be related to this.

Because of the possibility that DCA might improve body temperature and circulatory responses of unacclimatized men working in the heat by preventing or reducing the salt deficit developed during the first days of exposure, we made the salt intake of our subjects low so that the men would be likely to develop salt deficits. Absence of an effect of DCA on the men's body temperatures and heart rates during acclimatization to heat is not surprising then since it did not reduce the amount of salt deficit developed by the men. These results are in accord with those of Moreira *et al.* (5) who found that intravenous injections of adrenal cortical extract did not alter temperature regulation of fully acclimatized men working in the heat. Their subjects were acclimatized and on high salt intake and thus were always in adequate salt balance.

It is interesting that the unacclimatized men were capable in all cases of increasing their circulating blood volumes by the second or third hour of exposure on the first day in the heat and that administration of DCA showed no effect on this response. Since Clinton and Thorn (7) previously found that DCA increased men's blood volumes when they were resting in a cool environment it was thought possible that it might, by increasing blood volume, improve the circulatory responses and temperature regulation of unacclimatized men in the heat. The data indicate that this was not the case in our subjects.

SUMMARY

Four men, unacclimatized to heat, went through two series of 5 consecutive daily work experiments in a hot environment (50.5°C. with 15% relative humidity). Four days before the first exposure to heat in each series they began a constant diet containing 80 mEq. of chloride and 75 mEq. of sodium per day and continued on this diet throughout the 5 days in the heat. The men worked in pairs, one receiving intramuscular injections of desoxycorticosterone acetate (DCA) and the other acting as his own control for a later series in which he received DCA and the first man established a control. In the experimental series daily injections of DCA were begun 2 days before exposure to the heat and continued through the first day of exposure. At least 5 weeks during the winter season elapsed between the two series of experiments.

On the first exposure in each series the men showed the elevations of heart rate, body temperature, metabolism and sodium chloride concentration in the sweat which are characteristic of unacclimatized men working in hot environments. They underwent normal acclimatization during the 5 days of exposure with gradual reductions in all of the above measurements. Further evidence of acclimatization was a gradual rise in the average daily sweat secretion from 4.3 kg. the first day to 4.9 kg. the fifth day. During the first exposure there was an increase of 11 per cent in their blood volumes over control values determined in a cool environment.

Associated with the administration of DCA were higher concentrations of plasma sodium and lower concentrations of sodium and chloride in the men's sweat during the first 2 days in the heat. Under the conditions of these experiments none of the other measurements were significantly altered by exogenous DCA.

The authors are greatly indebted to Dr. Leo R. Radigan and Robert Long for their cooperation in the experiments and to Richard Mundy, Richard Shook, Vincent Canganelli and John Dragoo who served as subjects in the study.

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Age Changes in Rate and Level of Visual Dark Adaptation

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THE PURPOSE OF THIS STUDY was to determine the effects of aging upon the rate of visual dark adaptation. Previous studies have shown that the dark adapted eye declines in sensitivity in later life (1). It has been assumed that this lowered sensitivity is associated with a change in the rate of adaptation although this relation has not been demonstrated. No previous study has analyzed the *rate of adaptation* and the *level of adaptation* as independent functions which might change with age, although allusions have been made to an altered 'rate and amount' of adaptation in later life (2).

Several factors, e.g. pupil size, vitamin A deficiency, drugs and anoxia, are known to have an effect upon the minimum light threshold (3–8). Only the prior level of light adaptation, however, has been shown to affect the *rate* of dark adaptation (9, 10).

In none of the common pathologic conditions of the eye has there been noted an effect upon rate of adaptation (5) although the level of adaptation is affected, i.e. the minimum light threshold is elevated. In the aged there is an increase in retinal and macular degeneration and a correlated rise in the light threshold (11). If such lesions are similar in nature to those seen in young or middle-aged persons, presumably the rate of dark adaptation would be unaffected; conversely, if an altered rate of adaptation is observed in the aged it would reflect some process not associated with common retinal pathology. Thus it appeared that the comparison of the threshold level and the rate of change in the threshold was a potentially useful method of studying the basic nature of the aging process in vision.

PROCEDURE

A Hecht Shlaer adaptometer was used to measure the light threshold (12). The test field was circular 3°, exposed with violet light (below 460 mμ, Corning 511) for 0.2 seconds, and lay $7\frac{1}{2}°$ nasal to the fixation point. The light source was an incandescent lamp controlled by a voltage regulator.

Light thresholds were measured after three minutes of light adaptation at a brightness of 479 millilamberts. The pupils of all subjects were dilated with

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5 per cent euphthalmine prior to testing. This procedure fixed the pupil for both the light and the dark adaptation periods; all pupils dilated beyond 4 mm. Size of pupil was estimated by holding a millimeter scale beneath the eye. Values used in the present study were corrected to a standard 5 mm. pupil. The use of dilated pupils was the method of choice in this study because of the difficulties in the aged of keeping the eye centered with the use of an artificial pupil, and the greater relative error involved in measuring a miotic pupil. Threshold measurements were made at one-minute intervals for the first 10 minutes after exposure to bright light and at 2-minute intervals thereafter until a minimum of 30 minutes had elapsed.

The subjects were white and colored males from the Baltimore City Hospitals Home for the indigent aged and members of the William Hodson Community Center for the elderly in New York. All subjects were ambulatory and

TABLE 1. RATE AND LEVEL OF VISUAL DARK ADAPTATION IN SUBJECTS OF DIFFERENT AGE GROUPS

	AGE				AGE		
	40–59	60–69	70–83		40–59	60–69	70–83
Threshold at 6 min.				Cone rate of adaptation			
Mean[1]	5.26	5.64	6.04	Mean[2]	1.16	1.24	1.15
σ	0.59	0.45	0.43	σ	0.42	0.51	0.52
N	18	25	36	N	18	25	36
Threshold at 26 min.				Rod rate of adaptation			
Mean[1]	2.85	3.12	3.61	Mean[2]	4.39	5.58	5.41
σ	0.52	0.62	0.70	σ	1.02	1.60	1.63
N	19	28	35	N	19	27	35

[1] Values expressed in log $\mu\mu$ 1. [2] Values expressed as $K = \frac{dT}{dt}$; where T = log threshold and t = log of time.

non-hospitalized. A total of 91 subjects aged 40 to 83 years was included in this study.

The values for each subject were plotted on log-log graph paper in duplicate. Two investigators made independent graphic fits for each portion of the characteristic dark adaptation curve. The slopes of the graphic linear fit on the log-log paper were computed for each subject. Two independent estimates of the rate of cone and rod adaptation were thus obtained. The correlation between the slopes estimated by the two investigators was 0.90 ±.02 for both cone and rod adaptation rates. The mean of the two independent determinations was used as the best estimate of the rates of adaptation for each subject.

The data were analyzed to determine the correlation between age and the following variables: cone rate, 6-minute cone threshold, rod rate, 26-minute rod threshold. The correlations were also determined between the rates of cone and rod adaptation and the corresponding thresholds at 6- and 26-minutes.

The number of cases was not the same in each analysis of the results, as the number of observations varied. Thus, in some subjects it was difficult to obtain a complete enough set of data in the early part of adaptation to derive a rate of cone adaptation. Similarly, in other instances the curve was not complete enough in the latter phases of adaptation to derive a rate of rod adaptation.

RESULTS

There was little if any evidence in the present study that the rate of visual dark adaptation changed in later life (table 1, fig. 1). No significant correlation was found between age and the rates of cone and rod adaptation computed

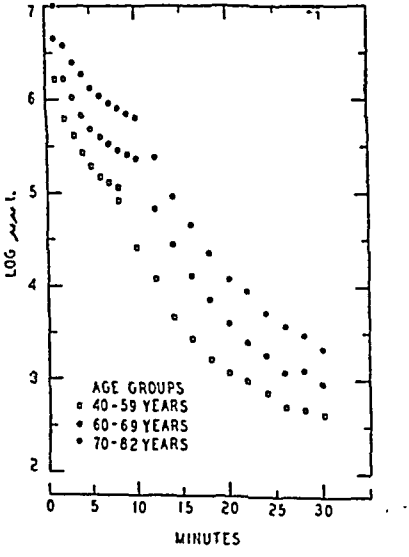

Fig. 1. DARK ADAPTATION CURVES of different age groups. Mean values computed from individual thresholds on comparable curve segments. Age 40–59, N = 22; age 60–69, N = 28; age 70–83, N = 41.

for each subject (table 2). The cone and rod thresholds, however, did show a significant correlation with age.

There was no relation between the thresholds and the rate of dark adaptation (table 2). In contrast, there was a significant correlation between the 6-minute and 26-minute thresholds; this correlation was 0.73 ±.06. Thus, these measurements were related despite the fact that the thresholds were presumably being measured on different segments of the dark adaptation curve, each with its own rate of change. This correlation, 0.73, is larger than the true relation due to the presence of a wide age range which inflates the variance. When age is extracted by means of a partial correlation, the correlation drops to 0.64.

There was a small increase in cone to rod transition time in the curves for the older subjects (fig. 1). A low positive correlation, 0.27 N = 75, was found between transition time and age. Since there was a tendency toward increased

individual differences in the rod threshold level in the older subjects, there exists the possibility of an older individual possessing the combination of a low cone threshold and high rod threshold. This combination would result in a delayed cone-rod transition time. Such a delayed transition time cannot be used as evidence of an altered rate of adaptation in the aged. Similarly the use of a test which measures the time required to reach an arbitrary brightness level should not be used to draw conclusions about rate of adaptation since the primary phenomenon in the aged is displacement of the threshold level.

SUMMARY AND CONCLUSIONS

The purpose of this study was to determine the effects of aging upon the rate and level of visual dark adaptation. Measurements of dark adaptation were made on 91 individuals aged 40 to 83 years. A Hecht Shlaer adaptometer was used to measure the light threshold at one- and 2-minute intervals for 30 minutes after a 3-minute period of light adaptation. The effect of reduced pupil size in the aged was eliminated from the data. The individual curves were plotted in duplicate and independent observers made graphic fits from which slopes of the curves were computed for each subject.

There was no correlation between age and either rate of cone adaptation or rate of rod adaptation. The cone threshold at 6 minutes and the rod threshold at 26 minutes were both significantly related to age. It appears that the lowered sensitivity of the aged eye is not accompanied by or results from a slower rate of adaptation. A tendency toward longer transition times between cone and rod vision appeared in the aged. The correlation between transition time and age was so low however as to require additional verification.

TABLE 2. CORRELATION BETWEEN DARK ADAPTATION MEASUREMENTS ON SUBJECTS AGED 30–40 YEARS

	6-MIN. THRESHOLDS	26-MIN. THRESHOLDS	CONE RATE	ROD RATE
age				
r	0.59	0.47	0.15[1]	0.24
N	83	86	83	86
6-min. Threshold				
r		0.73[2]	0.05[1]	
N		75	83	
26-min. threshold				
r				0.18[1]
N				86

[1] Not significantly greater than zero. [2] This correlation becomes 0.64 when the effect of age is removed by partial correlation.

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Changes in Renal Hemodynamics Associated with the Intravenous Administration of Sodium para-Aminohippurate[1]

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ALTHOUGH IT HAS BEEN PREVIOUSLY RECOGNIZED that the intravenous administration of sodium p-aminohippurate (PAH) in doses sufficiently large to permit the measurement of maximum renal tubular excretory ability (Tm_{PAH}) is attended by a number of untoward reactions, no alterations in renal hemodynamics have been demonstrated at high plasma PAH levels.

Chasis *et al.* (1) have noted that subjects receiving priming doses of PAH for Tm measurements experience sensations of warmth which occur in the absence of a rise in rectal temperature and occasionally complain of headache and nausea. Three of 43 patients receiving PAH intravenously vomited and two had formed bowel movements. They further noted that during the administration of the PAH priming dose, "the pulse rate and blood pressure remained unchanged." These observations were made on subjects who received an injection of 60 cc. of 20 per cent sodium p-aminohippurate at a rate of about 6 ml. per minute. Beyer *et al.* (2) have reported "intestinal and bladder smooth muscle response", manifested by defecation and micturation, when 50 cc. of 6 per cent PAH was injected intravenously over a period of 5 minutes. In subjects previously studied in this laboratory, complaints of intense, generalized body heat, headache and nausea were prominent during, and for a variable time following, the intravenous administration of 50 cc. of 20 per cent PAH. In addition to these subjective reactions, it has been observed that the glomerular filtration rate is frequently decreased during the measurement of Tm_{PAH}.

It was the purpose of this study to determine the changes in renal hemodynamics which occur at plasma levels of PAH sufficiently high to permit the measurement of Tm_{PAH}. In addition, the effect of the intravenous administration of PAH on pulse rate and blood pressure was investigated.

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METHOD

In 17 normotensive subjects free of clinical manifestations of cardiovascular and renal disease, who ranged in age from 22 to 69 years, the glomerular filtration rate (GF) was measured first during two or three urine collection periods during which the plasma PAH was maintained at levels of 0.9 to 3.0 mg. per cent and then during two or three periods in which the plasma PAH levels were maintained at 35 to 94 mg. per cent. These plasma PAH levels correspond respectively to levels commonly employed in the measurement of effective renal plasma flow and maximum tubular excretory ability.

In 10 of these 17 subjects, the renal plasma flow (RPF) was measured during both low and high plasma PAH levels. The RPF was determined by means of the Fick principle, using the PAH concentrations in the urine and plasma from both the femoral artery and the renal vein.

The following procedure was adhered to in all tests. After a no. 8 radiopaque intravenous catheter had been passed into the right renal vein under fluoroscopic observation and the clearance sustaining infusion of PAH and inulin had been maintained for 20 to 30 minutes, 2 to 4 urine collections were obtained by urethral catheter. Individual collection periods ranged from 10 to 15 minutes in duration, and simultaneous samples of blood from the renal vein and the femoral artery were withdrawn at the midpoint of each period. Immediately after these collection periods were completed, a Tm priming dose of 50 cc. of 20 per cent sodium p-aminohippurate was given intravenously over a period of 7 minutes, and after 20 to 30 minutes infusion of sustaining solution, 2 to 4 Tm_{PAH} urine collection periods were obtained. Again, blood samples from the femoral artery and renal vein were obtained simultaneously at the midpoint of each period.

Inulin was determined by Harrison's modification of the method of Alving (3). PAH determinations, using diluted urine samples and cadmium sulfate filtrates of plasma, were made by the method of Bratton and Marshall (4).

In an additional group of 10 subjects the pulse rate and blood pressure were recorded at minute intervals before, during and for 23 minutes following the intravenous administration of the aforementioned Tm priming dose of sodium p-aminohippurate.

RESULTS

Glomerular Filtration Rate. The mean GF for the 17 subjects decreased from 94.0 cc. per minute during the clearance periods to 81.9 cc. per minute during the Tm_{PAH} periods (table 1). This decrease is statistically significant ($N = 17; t = 3.99; P < .01$). Fourteen of the 17 subjects showed a decrease in GF; the mean decrease for these 14 subjects was 15.6 cc. per minute.

Renal Plasma Flow. The mean RPF for the 10 subjects who were studied with renal vein catheterization increased from 497 cc. per minute during clear-

ance periods to 567 cc. per minute during the Tm_{PAH} periods (table 1). This increase is significant ($N = 10; t = 4.10; P < .01$). The RPF increased in 8 of the 10 subjects; the mean increase for these 8 subjects was 91 cc. per minute.

Filtration Fraction. The mean FF for the 10 subjects studied with renal vein catheterization decreased from .181 to .145 (table 1). This decrease is significant ($N = 10; t = 9.2; P < .01$). It is important to note that the FF decreased in all of the subjects including the 3 subjects who showed no decrease in GF and the 2 subjects who showed no increase in RPF.

TABLE 1. COMPARISON OF GLOMERULAR FILTRATION RATE, RENAL PLASMA FLOW AND FILTRATION FRACTION AT LOW AND HIGH PLASMA PAH LEVELS

SUBJECT	AGE	GLOMERULAR FILTRATION RATE, CC/MIN.				RENAL PLASMA FLOW, CC/MIN.				FILTRATION FRACTION				PLASMA PAH, MG. PER CENT	
		A[1]	B[2]	Change	Per cent change	A[1]	B[2]	Change	Per cent change	A[1]	B[2]	Change	Per cent change	A[1]	B[2]
C. L.	50	82	48	−34	−41.5	655	670	+15	+2.3	.126	.071	−.055	−43.7	1.1	54.9
C. N.	60	113	87	−26	−23.0									2.8	59.5
P. D.	65	86	80	−6	−7.0	349	394	+45	+12.9	.255	.203	−.052	−20.4	1.8	54.8
A. A.	36	102	99	−3	−2.9									2.3	75.8
F. C.	45	102	88	−14	−13.7	611	717	+106	+17.3	.166	.124	−.042	−25.3	3.0	93.6
C. We.	57	84	70	−14	−16.7									2.3	68.7
A. D.	69	97	96	−1	−1.0	394	456	+62	+15.7	.245	.210	−.035	−14.3	2.0	59.5
E. N.	22	125	95	−30	−24.0									2.3	57.0
H. R.	50	107	89	−18	−16.8	655	813	+158	+24.1	.164	.111	−.053	−32.3	1.3	64.2
C. Wi.	61	91	86	−5	−5.5									2.6	76.1
R. B.	44	79	61	−18	−16.8	460	440	−20	−2.2	.172	.138	−.034	−19.8	2.7	94.4
E. H.	50	83	88	+5	+6.0	515	631	+116	+22.3	.162	.139	−.023	−14.2	1.5	82.6
R. N.	54	61	64	+3	+4.8	434	550	+116	+26.7	.141	.117	−.024	−17.0	2.9	65.7
J. B.	49	140	110	−30	−21.4									3.8	71.5
L. B.	23	102	107	+5	+4.9	588	700	+112	+19.0	.173	.153	−.020	−11.6	0.9	34.9
G. H.	67	79	70	−9	−11.3									4.7	64.0
D. Y.	55	65	54	−11	−16.9	309	295	−14	−4.5	.210	.184	−.026	−12.4	2.7	73.8
Mean	50.4	94.0	81.9	−12.1	−11.9	497.0	566.6	+69.6	+13.4	.181	.145	−.036	−21.1	2.43	67.70

[1] Low plasma PAH levels. [2] High plasma PAH levels. All values represent the mean of two to four urine collection periods. Values are not corrected for surface area.

Pulse Rate and Blood Pressure. In the second group of 10 subjects, 3 of whom (*P. D.*, *R. B.* and *E. H.*) were included in the RPF studies, the pulse rate and systolic, diastolic and pulse pressures increased in all cases during the administration of the Tm priming dose of sodium p-aminohippurate (fig. 1). The mean systolic blood pressure increased from 121 to 159 mm. Hg; the individual increases ranged from 20 to 71 mm. Hg. The mean diastolic pressure increased from 75 mm. Hg to 96 mm. Hg; the individual increases ranged from 11 to 40 mm. Hg. The mean pulse rate increased from 62 to 82; the individual increases ranged from 9 to 36. The mean pulse pressure increased from 45 to 63 mm. Hg; the individual increases ranged from 9 to 39 mm. Hg. The maximum elevation in individual pulse rate and blood pressure recordings occurred from 4 minutes to 8 minutes after the beginning of the injection and gradually decreased to

reach baseline values from 8 to 19 minutes following the completion of the injection of the PAH.

That this blood pressure and pulse rate response was peculiar to the PAH preparation used and not to the osmolarity of the solution is evident from the fact that the intravenous administration of 50 cc. of a sodium chloride solution of the same osmolarity (approximately 930 milliosmoles) at the same rate as the Tm_{PAH} priming dose caused no change in the pulse rate or the blood pressure of two subjects who responded characteristically to the Tm_{PAH} primer dose.

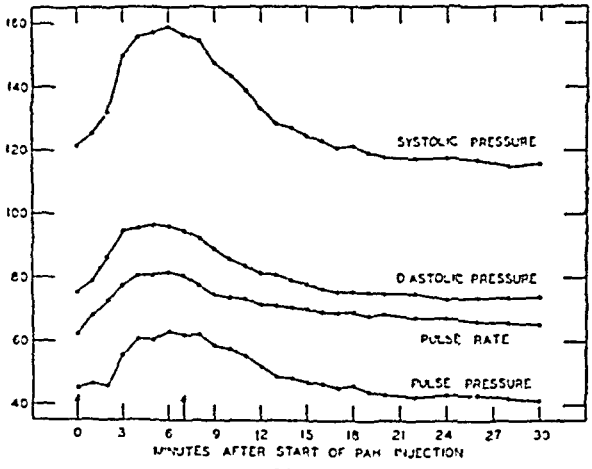

Fig. 1. MEAN VALUES FOR PULSE RATE and blood pressure in a group of 10 subjects. The beginning and end of an intravenous injection of 50 cc. of 20 per cent PAH are indicated by arrows.

DISCUSSION

It is apparent that the intravenous administration of PAH for the measurement of the maximal tubular excretory capacity of the kidney is accompanied not only by the unpleasant subjective reactions previously noted by others, but also by significant changes in cardiovascular dynamics generally and by alterations in the hemodynamics and vascular resistance of the very organ whose function is being measured.

From the information obtained in this study, several points of practical interest can be made. The observed decrease in GF with high plasma levels of PAH indicates that the GF value obtained during Tm_{PAH} measurements will, in the majority of cases, be spuriously low. Therefore, the GF value obtained at low plasma PAH levels should always be used, not only as an expression of an individual's baseline GF, but also in expressing the ratio of glomerular filtration per unit of functional tubular tissue (GF/Tm_{PAH}).

It has been demonstrated that the RPF is increased during the measurement of Tm_{PAH}. Unless high plasma PAH levels cause a diversion of part of the

renal blood flow through extra-tubular vessels, the tubular load of PAH during Tm periods as calculated from a previously determined effective renal plasma flow is approximately 15 per cent lower than the actual load.

The desirability of employing a substance other than PAH for the measurement of maximal tubular excretory ability is apparent. With this thought in mind, glomerular filtration rates with low and high plasma diodrast levels were compared in 105 subjects previously studied in this laboratory (5). In these subjects the GF decreased from 105.1 during diodrast clearance periods to 94.4 during Tm diodrast periods. This decrease in GF is of the same order as that which occurred with high plasma levels of PAH.

SUMMARY

The GF, RPF and FF were measured at low plasma PAH levels (0.9 to 3.0 mg. %) and at plasma levels sufficiently high to measure Tm_{PAH} (35 to 94 mg. %) in a group of 10 subjects. In a second group of 10 subjects blood pressure and pulse rate recordings were made at minute intervals before, during and for 23 minutes following the administration of a Tm_{PAH} priming dose (50 cc. of 20% sodium p-aminohippurate). At Tm_{PAH} plasma levels there was a significant decrease in GF and FF and a significant increase in RPF. During, and for several minutes following, the administration of the Tm_{PAH} priming dose, there occurred significant rises in blood pressure and pulse rate which returned to pre-injection levels within 30 minutes.

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Physiological Meaning of Regression Equations

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THE USE OF RELATIVE PHYSIOLOGICAL STANDARDS such as stroke volume per unit body weight or metabolic rate per unit of body surface or per unit of a power function of body weight, according to a recent article by J. M. Tanner (1) is "theoretically fallacious, and in practice (except under very special circumstances . . .) misleading." It seems useful to discuss the limitation of this pronouncement and to show that a physiologist's use of his reasoning power in general and of mathematics in particular should not stop with the formulation of an empirical regression equation.

CRITERION FOR THEORETICAL VALIDITY OF REGRESSION EQUATIONS

Tanner plotted the stroke volume of 50 men against their body weights. He noted that a linear regression equation with two empirically calculated constants ($y = a + bx$) fitted the observed data better than the simpler equation with only one empirical constant ($y = kx$). Tanner's observation agrees with the rather common knowledge that, as a rule, a line can be made to fit given data more closely the more empirical constants one is willing to calculate and use for the construction of the line.

The question is whether or not an equation is theoretically fallacious because it fits a set of empirical data less closely than another equation does. I shall attempt to show that of two equations expressing physiological relations, one may be theoretically preferable even though it fits a given set of empirical results less than the other; that is, leads to a larger sum of squared deviations between calculated and observed result. From the point of view of statistical theory, this may be sheer heresy, but I presume that 'theoretical' here means pertaining to theory in physiology. Among various equations relating two physiologically important variables, the one which gives the simplest, clearest and most general expression for this relation is theoretically the best. Of course the calculated result has to express the facts and thus fit the observations, but the accuracy of fit is not the only criterion for the theoretical value of an equation. Copernicus' equations for the movement of heavenly bodies may actually have been less accurate for predicting positions of planets than Ptolemy's older equations, but Copernicus' calculations were simpler and

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particularly more general, permitting the inclusion of celestial phenomena in a general theory of gravitation and motion. That made Copernicus' equations theoretically more valuable.

EXAMPLE IN GEOMETRY

Orthodox belief that an empirical regression equation is the best solution of a problem may prevent the search for a theoretically better one. An example from geometry may illustrate this point. The measured surface areas of a set of spheres may be plotted against the volumes as in range *A* of figure 1. An empirical linear regression equation

$$S = 15.1 + 1.04\ V \qquad (1)$$

may be the statistically best expression for the relation between surface area and volume of these spheres. Considering the errors of measurement there may be no point in trying a curvilinear regression, since a resulting decrease in the sum of squared deviations may be statistically insignificant. For practical purposes, namely the prediction of an average surface area for a sphere of given volume within the range considered, the equation may be satisfactory.

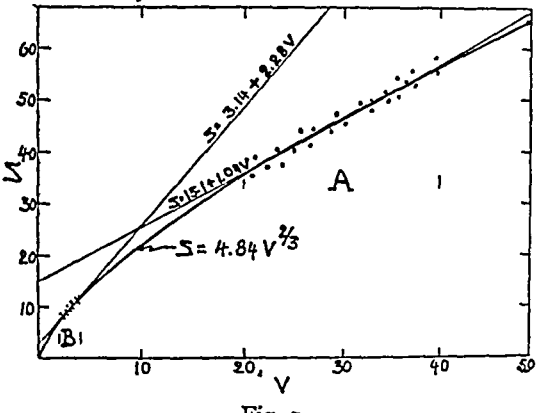

Fig. 1

The geometer, however, may be bothered by noticing that his equation predicts a definite surface area of 15.1 for a sphere without volume. Being theoretically inclined, he may not be satisfied with Dr. Tanner's declaration that this is beside the point. This dissatisfaction may stimulate the geometer to measure the surface areas and volumes of a set of smaller spheres and plot the results as in range *B* of figure 1. The empirical regression equation for this set may be

$$S = 3.14 + 2.28\ V \qquad (2)$$

Again a sphere without volume appears to have a definite surface area, but different from that of the other set of spheres.

The theoretically inclined geometer is still more dissatisfied by the different expressions for the relation of surface area to volume of his two sets of obviously similar objects. He may suspect that not getting generally valid coefficients out of his observations indicates unsuitable dimensions in his equations. In his drive for a more general formulation, the geometer may try several mathematical operations. One of these, namely plotting the logarithm

of the surface area against the logarithm of volume, distributes the data of the two sets of spheres along a straight line expressed by the equation

$$\log S = 0.684 + 0.67 \log V \qquad (3)$$

which indicates the following relation:

$$S = 4.84\ V^{\frac{2}{3}} \qquad (4)$$

This last equation is theoretically preferable to the empirical regression equations even if each of these empirical equations should lead to smaller sums of squared deviations for the particular set of spheres for which it is calculated. *Equation 4* is generally valid and reasonable (for example gives a zero surface for a zero volume). Its terms have geometrical meaning. The power function $\frac{2}{3}$ expresses the general relation of areas to volumes in bodies of any given shape. The parameter 4.84 is a characteristic for spheres (the specific surface of a unit volume sphere); the corresponding term for cubes is 6.00. The general formulation of the surface area of bodies in terms of volume is $S = KV^{\frac{2}{3}}$ where K is constant within any group of similarly shaped bodies. In biology the specific surface of a unit volume body, K, is often called the Meeh constant. For most mammals it is roughly 10.

EXAMPLE IN PHYSIOLOGY

To demonstrate that the geometric example is a valid, though simplified, illustration of the problem under discussion, an example from the realm of physiology follows. Harris and Benedict (2) derived for the metabolic rate of 136 men the following empirical regression equation:

$$M = 66.4730 + 13.7516\ W + 5.0033\ h - 6.755a \qquad (5)$$

where M = total heat production in Cal. per 24 hr., W = body weight in kilograms, h = height in centimeters, a = age in years.

This regression equation is statistically 'the best' and for practical purposes, such as comparing a man's metabolic rate with an empirical standard, it serves well. Theoretically, however, it is unsatisfactory, like the empirical regression *equations 1* and *2* for the relation of surface and volume of spheres, and for the same reason. The physiologist is bothered by an equation which predicts a definite metabolic rate for a weightless man and whose other terms are physiologically meaningless. Krogh has already criticized this equation for that reason (3).

Like the geometer in the example above, Kleiber (4, 5) has attempted to find a more general and thus theoretically more valuable expression for the relation of body size and metabolic rate in man. Like the geometer, he used a set of smaller objects to derive the general trend (choose the most suitable dimension of the variable). The logarithm of metabolic rate for various ani-

mals from rat to steer plotted against the logarithm of the respective body weights indicated a linear relation which led to the equation

$$M = KW^{\frac{3}{4}} \qquad (6)$$

similar to the one for the surface of spheres. In contrast to the surface-volume problem, there was for metabolic rate no compelling theoretical reason to use a given exponent. The empirically best fitting among simple exponents ($\frac{3}{4}$) was therefore chosen for calculating the metabolic rate of the 136 men of Harris and Benedict as follows:

$$M = 71.2\ W^{\frac{3}{4}}\ [1 + 0.004\ (30\text{-}a) + 0.01\ (\frac{h}{W^{\frac{1}{3}}} - 43.4)] \qquad (7)$$

where the letters have the same meaning as in the Harris-Benedict equation above.

The terms of *equation 7* have a definite physiological meaning. The exponent $\frac{3}{4}$ expresses the general trend in the relation of metabolic rate and body weight obtained from results on animals which differ greatly in size (interspecific comparison), the factor 71.2 characterizes the particular metabolic level of the 136 men in comparison to other homeotherms, for example to 103 women whose mean metabolic level was 67.4 Cal. per unit of the $\frac{3}{4}$ power of body weight, or 48 female rats between 230 and 300 days of age (98 measurements) whose mean metabolic level was 73 Cal/kg.$^{\frac{3}{4}}$ (5). The factor in parentheses indicates the changes in metabolic rate resulting from difference in age and specific stature between individuals. Each year deviation from the mean age of 30 produces 0.4 per cent change in the metabolic level, and a change of one unit of specific stature ($\frac{h}{W^{\frac{1}{3}}}$) from the mean of 43.4 changes the metabolic level one per cent. (The age term might be made more general by expressing age as a ratio to some standard instead of expressing it in years.) Since thus *equation 7* conveys more physiological meaning than *equation 5*, it is theoretically preferable.

PHYSIOLOGICAL SIGNIFICANCE OF COEFFICIENTS

As in the example above, empirical regression equations often fail to satisfy the theoretical inclination of the physiologist. In this case, he should try to find a theoretically better, physiologically more meaningful, expression. That means recalculating the raw data. Following Dr. Tanner's advice for preventing a fallacy, he may try to find out whether, for any one value of one variable, the raw values of the other variable or the logarithms of them are more nearly normally distributed. As a rule he may notice that the number of his measurements is much too small to establish for a given X a significant difference between the skewness of the distribution of Y and the skewness

of the distribution of log Y. In this predicament he may be relieved by reading the following statement of Yule and Kendall (6): "The answer to the question whether the correlation between indices or that between absolute measures is misleading depends on the further question whether the indices or the absolute measures are the quantities directly determined by the causes under investigation."

This statement of eminent statisticians moves responsibility and priority from the calculating machine back to the physiologist who thinks in terms of physiological relations ('causes') rather than skewness of distribution in his particular sample.

Often the generality, and thus the theoretical value of an expression, can be established only empirically. An example is the 3/4 power of body weight as a generally suitable measure of body size for expressing metabolic rate of mammals. In many cases, however, the most general term may be chosen *a priori* such as the 2/3 power of volume for expressing surface areas of bodies.

Comparative physiology is based on the fundamental postulate that animals are comparable and thus more or less similar. This similarity offers the basis for comparing build and function of various animals; in particular animals of different size. The most effective terms for comparing form and function of various animals are those which would remain constant for changing size if large and small animals were strictly similar. Such terms are ratios of equidimensional quantities such as $\frac{\text{length}}{\text{volume}^{\frac{1}{3}}}$; $\frac{\text{surface}}{\text{volume}^{\frac{2}{3}}}$; $\frac{\text{volume}}{\text{volume}}$, or, for given specific gravity, also $\frac{\text{length}}{\text{weight}^{\frac{1}{3}}}$ or $\frac{\text{surface}}{\text{weight}^{\frac{2}{3}}}$ or $\frac{\text{volume}}{\text{weight}}$.

The ratio $\frac{\text{plasma volume}}{\text{surface area}}$ may statistically express a relation within a limited material, but the statement of Dreyer, Ray and Walker (7) that "the practice of expressing blood volume as a percentage of body weight is both erroneous and misleading" is, from the point of view of comparative physiology, unacceptable. The statement that the blood volume of mice amounts to 0.149 ml/unit surface area, that for guinea pigs 0.189, and that for rabbits 0.632, has little specific significance for comparison because even in strictly similar animals differing in size as much as mice, guinea pigs and rabbits, there would be an analogous change in the blood volume per unit of surface area. In this ratio, therefore, size effects per se are superimposed on specific group effects. On the other hand, the statement that the blood volume of mice was 5.8 per cent of the body volume, that of guinea pigs 4.1 and that of rabbits 4.9 per cent, has direct comparative significance, since among similar animals that differ in size the percentage of blood volume would remain constant. The percentages given thus indicate directly the degree of similarity between

groups of animals with regard to the variable in question. One may say, for example, that in this case guinea pigs had a relatively smaller blood volume than rabbits or mice.

An analogous consideration applies to stroke volume as a function of body size. In similarly built and functioning animals of different size the stroke volume per unit body volume, or per unit body weight, would be constant (being a ratio of equidimensional terms). On the basis of the similarity principle, therefore, the stroke volume per unit weight indicates directly whether a given set of mice have a smaller or larger relative stroke volume than a given set of men. The ratio $\frac{\text{stroke volume}}{\text{body weight}}$ is thus physiologically more revealing, and therefore theoretically more valuable, than an empirical regression equation whose terms have no physiological meaning. Dr. Tanner's (1) empirical regression equation is interesting because it indicates that within his set of 50 men the stroke volume, as a function of body size, deviates from the trend expected on the basis of similarity between large and small men. Whether or not this deviation is statistically significant, unfortunately, cannot be judged from the data given in the article. Assuming that the deviation from the similarity trend is statistically significant, it would be physiologically valuable to discover the factors that produce this deviation. Such a discovery would be unlikely if one would accept the pronouncement that the empirical regression equation is the best expression for stroke volume and body weight, and that any other, such as the stroke volume per unit weight, is theoretically fallacious and in practice misleading.

Advocating the use of ratios of equidimensional terms for expressing anatomical and physiological relations, in preference to less intelligible ratios of terms with different dimensions, does not declare the use of these other ratios as fallacious. The term 'specific surface' $(\frac{\text{surface area}}{\text{volume}})$ for example, has its proper place in colloid chemistry, even though it combines (and confounds) size and shape functions. The term 'metabolic rate per unit weight' is justified for expressing the mean metabolic intensity in the tissues of animals. The metabolic rate per unit surface area, or $(\text{body weight})^{\frac{2}{3}}$, has its proper place when questions of heat transfer are studied; whereas the metabolic rate per unit of the 3/4 power of body weight is most suitable for characterizing an animal's metabolic level in comparison with other homeotherms.

SUMMARY

The theoretical significance of empirical regression equations expressing physiological relations is, as a rule, limited. Such equations should therefore be a start, rather than an end, to a physiologist's further reasoning and calcu-

lating. Two examples are discussed to illustrate this point. The principle of similarity offers a good basis for expressing relations of anatomical and physiological variables to body size by equations whose terms have a biological meaning. In general, ratios of equidimensional terms furnish the simplest and most general expressions for physiological relations. Other ratios are, however, also justified and may be best suited for particular problems.

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Human Sensitivity to a Standardized Cold Test[1]

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ABRAHAMSON BELIEVES that the skin response to exposure to cold may be due to physical allergy. Urticaria or wheal formation is produced easily in some individuals while in others it requires more severe exposure. Abrahamson believes the whealing response does not occur in normal skin (1). This is probably incorrect. Many observers have produced wheal formation and also gangrene in animals, including man, by increasing the severity of the exposure (2, 3).

Marked variation in the response of animals to a standard exposure to cold has previously been described (1, 4, 2). Lange has described this variation in humans. He states that the response of any one subject is rather constant (3). In fact, Lange and co-workers suggested in 1947 that it might be possible to screen persons with an unusually high sensitivity to cold by means of a standard cold test.

The purpose of these experiments was to ascertain whether it is feasible to determine a person's sensitivity to cold by means of a standardized cold test.

METHODS

Two glass cylinders were prepared, one smaller than the other, so the smaller would fit loosely inside the larger (fig. 1). The one with the smaller bore was about 5 inches in length and the one with the larger bore was about 4 inches in length. The inner cylinder was then fitted with a cork stopper at each end. The apparatus was then charged with solid CO_2 in the following manner. A no. 6 standard cork borer was gently heated over a flame and when warmed was pressed firmly down upon a large block of solid CO_2 about 1 inch in thickness, just as the housewife cuts cookie dough with a mold.

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Care was taken not to press too firmly as the CO_2 cracked easily. It was usually necessary to heat the cork borer several times in cutting a single cylinder of CO_2. The tip of a common household sewing needle was then heated and a hole burned through the cylinder of CO_2 about $\frac{1}{3}$ the distance from the end. The same needle was then threaded and the cylinder of CO_2 sewed to one cork (as shown in the lower cork of fig. 1). The thread was then passed through the small glass cylinder, the lower cork inserted, the thread pulled taut and the upper cork inserted. The lower end of the cylinder of snow was then inspected and if rough or uneven was easily smoothed off by placing the side of a warmed spatula on, and perpendicular to the cylinder of CO_2.

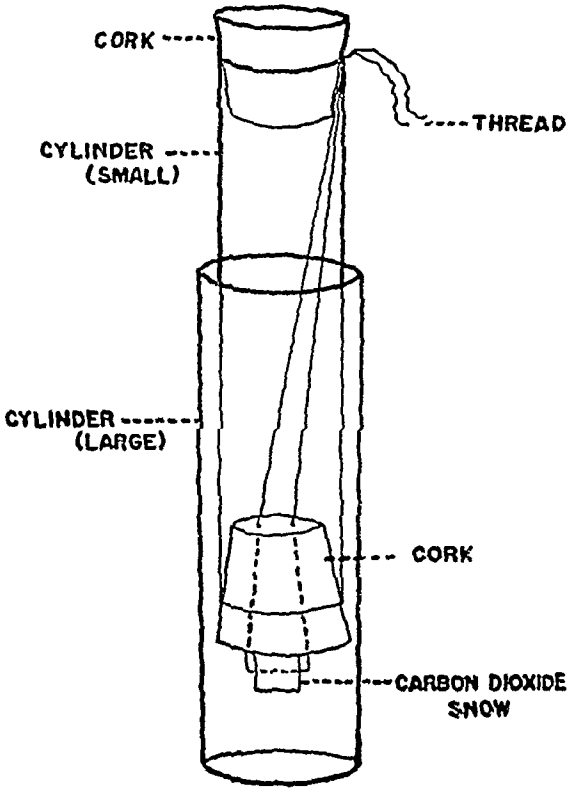

Fig. 1.

USE OF THE APPARATUS

The subject bared the anterior surface of the forearm and held it horizontal. The large cylinder was then placed on the anterior surface of the forearm which was free from hair and superficial vessels. The smaller cylinder with the CO_2 attached was placed inside the larger cylinder and held so the CO_2 was about $\frac{1}{2}$ inch above the arm. At a signal from an assistant with a stop watch, the smaller cylinder was released letting the CO_2 come to rest on the subject's skin. After two seconds, at a second signal from the assistant, the CO_2 was quickly removed. It was important that the small inner cylinder be free and not held during the two seconds as the cylinder plus the corks and CO_2 weighed exactly 16.5 grams, and only if it remained free inside the larger cylinder could one be assured that the same weight was applied to each test. It was necessary to recharge the smaller cylinder with CO_2 after about 10 minutes of use due to its decrease in size and weight caused by sublimation.

The reaction was then interpreted 5 to 10 minutes following the application and was graded as follows (all interpretations being made by the same observer):

a. No reaction. Erythema without wheal formation.

b. Reaction 1+. Any wheal formation less than 25 per cent of area covered by CO_2.

c. Reaction 2+. Any wheal formation more than 25 per cent but less than 50 per cent of area covered by CO_2.

d. Reaction 3+. Any wheal formation more than 50 per cent but less than 100 per cent of area covered by CO_2.

e. Reaction 4+. Any wheal formation of 100 per cent or more of area covered by CO_2.

On the first, second, third and fourth of March 1949, 116 white males, ranging in ages from 17 to 47, were subjected to a standardized cold test. Solid CO_2 was applied to the anterior aspect of the forearm over an area of 0.8 to 1.0 cm. in diameter with a pressure of 16.5 grams for a duration of two seconds. The mean temperatures on the first, second, third and fourth of March were 47°, 52°, 53°, and 56° respectively. The low humidity and high humidity on the same days were 61, 98; 46, 90; 36, 89; and 48, 94 respectively. On the first, second and third of June 1949 these same men were retested in a similar manner. The mean temperatures on the first, second, and third of June 1949 were 85°, 84°, and 83° respectively. The low humidity and high humidity on the same days were 33, 93; 36, 90; and 40, 95 respectively.

RESULTS

Discounting the 1+ reactions as questionable responses and evaluating only those of 2+ or more, the following was noted. The 14 reactors in March were retested in June under different climatic conditons. Of these 14, only 4 now gave a similar response (2+ or greater reaction). The remaining 10 reacted with only an erythema or 1+ response. In the June test there were 25 reactors (2+ or greater response), only 4 of whom were reactors in March. There were 21 who gave a 2+ or greater response, who in March had given only a 1+ or an erythematous response.

The reactors and non-reactors of the total group of 116 are sorted in table 1 into a contingency table. The χ^2 test as developed by Karl Pearson (5) shows that the overlap in reactors at the two times, March and June, could have happened by random sampling. Thus the test is unreliable as it is not reproduceable in the same individual (table 1).

While data were taken primarily to determine the reliability of the test, it was convenient to record certain other facts relating to personal history such as history of previous frostbite, sweating, history of allergy, nature of skin, and home locality (north or south of the Mason-Dixon Line) in order to determine whether there was any association between these facts and sensitivity to cold as determined by the present skin test.

Lewis and Love (2) in 1926 believed that this variation in response of

different individuals had to do in part, at least, with the oil content of the skin. Lake was also aware of this phenomenon. Ungley *et al.* (6) believed that hyperhydrosis accompanied increased cold sensitivity. The following is the association study of the June testing.

Frostbite History. Ten of the 116 individuals gave a history of previous mild frostbite. Three of these were reactors while 7 were non-reactors (table 2). Application of the χ^2 test indicates no correlation between previous mild frostbite and the described test.

TABLE 1. CONTINGENCY TABLE OF RELIABILITY OF THE TEST

		June			
		Reactor	No Reactor		
March	Reactor	4	10	14	$\chi^2 = .478$
	No Reactor	21	81	102	$df = 1$
		25	91	116	$P = .49$

χ^2 = Sum of all contributions. df = Degree of freedom. P = Probability of sample when in reality there is no association.

TABLE 2. CONTINGENCY TABLE FOR FROSTBITE

	Frostbite	No Frostbite		
Wheal	3	22	25	$\chi^2 = .4077$
No Wheal	7	84	91	$df = 1$
	10	106	116	$P = .33$

TABLE 3. CONTINGENCY TABLE FOR SWEATING

	Low	Normal	High		
Wheal	2	16	7	25	$\chi^2 = 1.7934$
No Wheal	2	62	27	91	$df = 2$
	4	78	34	116	$P = .42$

Sweating. Four of the 116 had hypohidrosis, 78 normal hidrosis and 34 hyperhidrosis. Of those with hypohidrosis 2 were reactors and 2 were non-reactors. Of those with normal hidrosis 16 were reactors and 62 non-reactors. Of those with hyperhidrosis 7 were reactors and 27 non-reactors (table 3). Application of the χ^2 test indicates no correlation.

Allergy. Five of the 116 gave a history of some form of allergy. Only one of these 5 was a reactor while 4 were non-reactors (table 4). Application of the χ^2 test indicates no correlation.

Nature of Skin. Three of the 116 had dry skin, 98 normal skin and 15

oily skin. Of those with dry skin one was a reactor while 2 were non-reactors. Of those with normal skin 22 were reactors and 76 non-reactors. Of those with oily skin 2 were reactors and 13 non-reactors (table 5). Application of the χ^2 test indicates no correlation.

Home Locality. Of this 116, there were 57 from the North and 59 from the South. Of those from the North 15 were reactors while 42 were non-reactors. Of those from the South 10 were reactors while 49 were non-reactors (table 6). Application of the χ^2 test indicates no correlation.

Association studies of the March tests showed completely analogous results.

TABLE 4. CONTINGENCY TABLE FOR HISTORY OF ALLERGY

	Allergy	No Allergy		
Wheal	1	24	25	$\chi^2 = .00989$
No Wheal	4	87	91	$df = 1$
	5	111	116	$P = .92$

TABLE 5. CONTINGENCY TABLE FOR NATURE OF SKIN

	Dry	Normal	Oily		
Wheal	1	22	2	25	$\chi^2 = .956$
No Wheal	2	76	13	91	$df = 2$
	3	98	15	116	$P = .63$

TABLE 6. CONTINGENCY TABLE FOR HOME LOCALITY

	North	South		
Wheal	15	10	25	$\chi^2 = 1.48$
No Wheal	42	49	91	$df = 1$
	57	59	116	$P = .23$

Greene (2) has suggested that possibly cold agglutinins might enter into the response in some way. Three of the individuals who gave a positive response (2+ — 4+) on both the March and June tests and 3 individuals who were negative (an erythema only) on both tests were investigated for cold agglutinins. All 6 were negative for cold agglutinins.

CONCLUSIONS

The variation in response to the described test by individuals was great and variation in response of the same individual within a 3-month period was equally great. The statistical analysis indicates that all reactors may be

explained by chance alone. A field test would, therefore, not be indicated. Previous frostbite, sweating tendencies, allergy, home locality and nature of skin are not correlated with cold hypersensitivity as evaluated by the described test. In this study the sample size was adequate, and there were no borderline probabilities.

The author wishes to express appreciation to Dr. J. A. Rafferty, Chief, Department of Biometrics, Randolph Army Air Field, Texas, for the statistical analysis.

The photographs are BGH USA negative number 5395.

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Blood Picture at High Altitude

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SINCE THE TIME OF PAUL BERT, it is a well known fact that low barometric pressures evoke changes in the blood picture. These changes have been studied by a great number of authors, but it is only recently that a complete study of the effects of altitude chronic hypoxemia upon the hemopoietic activity was made by Hurtado and co-workers (1). Their paper contains a review of the subject.

The new laboratories of the Instituto de Biologia de la Altura at Mina Aguilar[1] (3975 and 4515 m. above sea level) have made possible a study of the blood picture of people living at the place; the results are published in this paper.

METHODS

In all cases blood was drawn in the morning, while the subjects were in fasting conditions. In the cases in which arterial blood was secured, the subjects had a previous rest of at least half an hour. Venous blood, obtained without stasis and transferred to a tube containing ammonium oxalate and potassium oxalate, was used for hemoglobin, hematocrit, and red and white cell determinations. For the sedimentation rate, 2.6 ml. of venous blood were drawn in a syringe containing 0.6 ml. of a 3.8 per cent sodium citrate solution.

Arterial blood was obtained under liquid paraffin from the femoral artery, dried 'Liquemin' Roche being used as anticoagulant.

Hemoglobin. Duplicate determinations were made in a Sahli hemoglobinometer, previously calibrated by the oxygen capacity method; in eight subjects, determinations with both methods were made.

Red and white cell counts. Two counts were always made and the average taken as the final result.

Hematocrit. Blood transferred to a Wintrobe tube was centrifuged for one hour at 3500 r.p.m. In a number of cases, duplicates were made. No correction for the shrinkage resulting from the use of a mixture of ammonium and potassium oxalates to avoid clotting was made.

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[1] The facilities granted to the Institute and its staff by the Compania Minera Aguilar are gratefully acknowledged.

Differential count. Capillary blood from a finger was used, smears being stained with May-Grunwald-Giemsa.

Sedimentation rate. The Westergren method was employed, with readings taken at the first hour; temperature ranged between 19 and 21 degrees C.

Arterial saturation. It was determined according to the technique of Dill and co-workers (2).

RESULTS

Observations were made on 84 subjects, in good health, who lived permanently at 4515 m. above sea level. The average barometric pressure was 456 mm. Hg. The subjects had been living at the place from 3 months to 57 years; they never left it for more than one or two months in the year. Except in a few cases, all subjects were born in the high Andean altiplano. Their physical characteristics were: average height, 1.62 m.; average weight, 64.3 kg.; age, from 20 to 57 years, although only seven persons were older than 45. None of them gave a history of pneumonoconiosis.

TABLE 1. ARTERIAL OXYGEN SATURATION IN MEN LIVING PERMANENTLY AT MINA AGUILAR

ALTITUDE	AVERAGE BAROMETRIC PRESSURE	NO. OF SUBJECTS	ARTERIAL OXYGEN SATURATION		
			MEAN ± S.E.	S.D.	RANGE
4515 m.	445.8 mm. Hg	7	80.6 ± 1.57	±3.84	74.7–86.2

In seven subjects, arterial oxygen saturation averaged 80.6 ± 1.57 per cent with extreme values of 74.7 and 86.2 (table 1); about the same values were obtained by Hurtado and co-workers on 18 subjects living at Morococha (4540 m.).

The average for hemoglobin values was 19.4 ± 0.22 gm. per cent, in 67 subjects, ranging from 15.7 to 24.9; for red cells, 6.46 ± 0.09 million per cu. mm. in 84 subjects, with extreme values of 5.07 and 9.93, and for hematocrit readings, 59.5 ± 0.58 per cent in 81 subjects, with extreme values ranging from 50.5 to 73.6 (table 2). All these figures show an evident increase over those obtained by Moglia and Fonio (3) in normal males living at Tucuman (427 m.), while mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration agree fairly well (tables 2 and 3).

As is shown in figure 4, there is an inverse correlation between red cell number and mean corpuscular volume; the coefficient of correlation is .69 ± .06, the difference from zero being 11.5 times its standard error; and therefore the coefficient of correlation is statistically significant.

In figures 1, 2, and 3, hemoglobin, hematocrit, and red cell values have been plotted against years of continuous residence at 4515 m. Wide variations

can be observed among individuals who lived at the place for the same length of time. No relation seems to exist between duration of hypoxia and degree of

TABLE 2. BLOOD PICTURE OF MEN LIVING PERMANENTLY AT MINA AGUILAR (4515 m).

DETERMINATIONS	NO. OF SUBJECTS	MEAN ± S.E.	S.D.	COEFF. OF VARIATION	RANGE
				%	
Red cells, $\times 10^{-6}$	84	6.46 ± 0.09	±0.82	13	5.07– 9.93
Hematocrit, red cells, %	81	59.5 ± 0.58	±5.2	9	50.5 – 73.6
Hemoglobin, gm. %	67	19.41 ± 0.22	±1.80	9	15.66– 24.95
Mean corpuscular volume (cu. μ)	81	92.4 ± 0.89	±7.99	9	74.2 – 110.9
Mean corpuscular hemoglobin ($\mu\mu$g.)	66	29.9 ± 0.26	±2.11	7	25.1 – 35.8
Mean corpuscular hemoglobin concentration, %	66	32.7 ± 0.16	±1.31	4	28.5 – 35.6
Sedimentation rate, mm. in the 1st hour	70	0.71 ± 0.10	±0.81	114	0.05– 3.8
Leucocytes	83	6744 ± 198	±1804	27	4100 –12,100
DIFFERENTIAL COUNT					
Neutrophils, segmented, %	73	44.1 ± 1.29	±11.0	25	13 – 69
Neutrophils, stab, %	73	6.3 ± 0.48	±4.1	65	1 – 16
Neutrophils, total, %	73	50.4 ± 1.38	±11.7	23	16 – 75
Eosinophils, %	73	2.9 ± 0.32	±2.7	93	0 – 14
Basophils, %	73	0.8 ± 0.05	±0.4	50	0 – 3
Lymphocytes, %	73	35.6 ± 1.19	±10.1	28	8 – 55
Monocytes, %	73	10.2 ± 0.62	±5.3	52	2 – 33

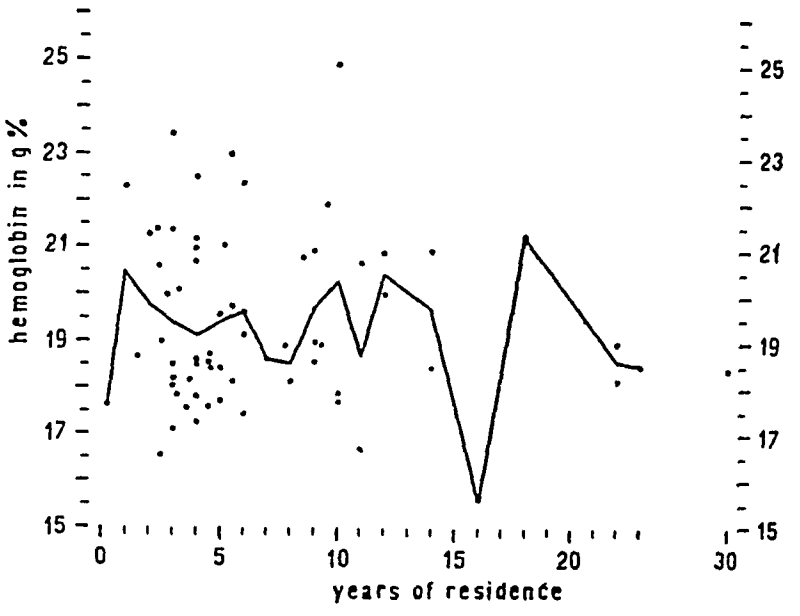
TABLE 3. BLOOD PICTURE OF MEN, 20 TO 44 YEARS OLD, LIVING IN TUCUMAN (427 m.) AS DETERMINED BY MOGLIA AND FONIA (1944)

DETERMINATIONS	NO. OF SUBJECTS	MEAN ± S.E.	S.D.	COEFF. OF VARIATION	RANGE
				%	
Red cells, $\times 10^{-6}$	153	5.31 ± 0.03	±0.42	8	4.54– 6.78
Hematocrit, red cells, %	153	48.7 ± 0.24	±3.0	6	41.6 – 59.4
Hemoglobin, gm. %	153	16.12 ± 0.09	±1.14	7	13.5 – 18.7
Mean corpuscular volume, cu. μ	153	91.9 ± 0.46	±5.66	6	76.9 –108.3
Mean corpuscular hemoglobin, $\mu\mu$g	153	30.4 ± 0.16	±1.97	6	26.4 – 34.9
Mean corpuscular hemoglobin concentration, %	153	33.2 ± 0.14	±1.72	5	29.2– 37.5

hemopoietic response. As it is shown by the coefficient of variation, the individual variations are greater than at sea level.

In the first hour, the average sedimentation rate was 0.71 ± 0.10 mm., which is lower than that found in the normal man at sea level. The average

value of leucocytes per cu. mm. was 6744 ± 198, extreme values ranging from 4100 to 12,100. Differential counts showed slight increases in the lymphocyte



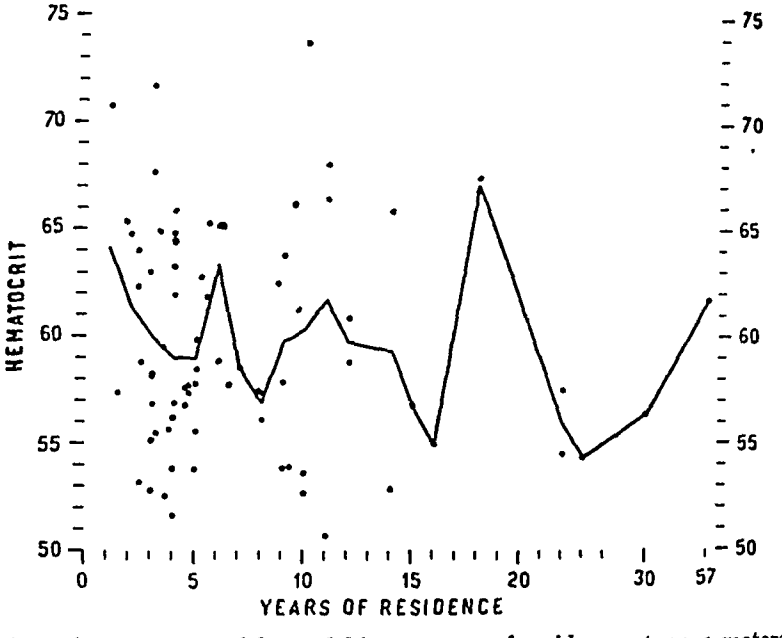


Fig. 1. (*upper*). RELATION of hemoglobin to years of residence at 4515 meters. (It will be noted that only three values fall below 17 gm. per cent.)

Fig. 2 (*lower*). RELATION of hematocrit to years of residence at 4515 meters. (It will be noted that all values are above sea level average.)

and monocyte percentages with a correlative diminution of neutrophils. In some cases, the increase of lymphocyte percentage was striking.

Fig. 3. RELATION of red cell count to years of residence at 4515 meters.

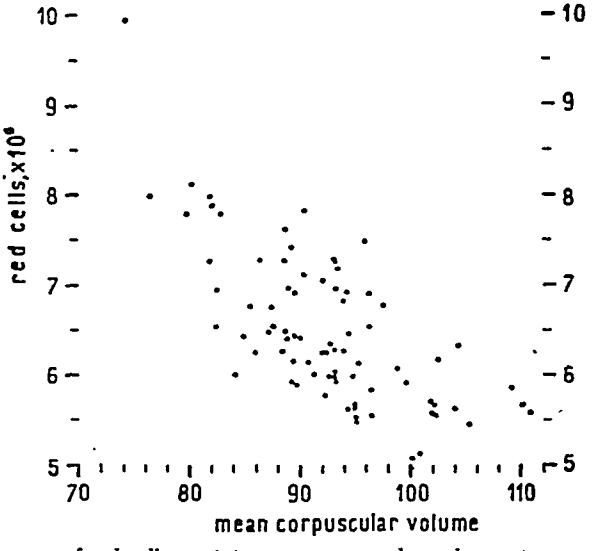


Fig. 4. RELATION of red cell count to mean corpuscular volume at 4515 meters.

DISCUSSION

Chronic hypoxemia caused by residence at 4515 m. above sea level produces in man an increase of the average values of hemoglobin, red cells, and hematocrit and a decrease of the average sedimentation rate of the erythrocytes. Although no changes were found in the number of leucocytes, a relative increase of monocytes and lymphocytes was observed.

Hemoglobin, red cell, and hematocrit figures are scattered within wide limits. No relation was found between length of permanent residence at 4515 m., that is, duration of hypoxia, and degree of change in blood picture. Thus, a great increase in hemoglobin takes place within the first year of residence at that altitude and, in rare cases, almost normal values after ten years, as already pointed out by Monge (4).

Such variability in the hemopoietic response to a same degree of barometric depression could be due to: *a*) a widened range of the normal individual variations found at sea level; *b*) the different degree of hypoxemia found in the subjects living at the same altitude, the response of the hemopoietic system being proportional to the intensity of the hypoxemic stimulus; and finally, *c*) some unknown factor, which would make a great increase of the hemoglobin less necessary for the adaptation of the human body to chronic hypoxemia.

The mean corpuscular volume and the mean corpuscular hemoglobin did not show any significant deviation from the normal values found at sea level; the polycythemia was normocitic, in opposition to the findings of Hurtado and co-workers (1).

Our average figures of red cells, hematocrit readings, and leucocytes agree with those obtained by Hurtado and co-workers (1) in subjects of similar racial and physical characteristics, living at 4540 m. and with an almost coincident arterial oxygen saturation. On the other hand, the hemoglobin average is 1.35 gm. lower in our subjects.

The observed decrease of the sedimentation rate of the red cells can be ascribed, in part at least, to the polycythemia.

SUMMARY

A study of the blood picture of normal subjects living permanently at 4515 m. above sea level has been made. The hemoglobin, red cell, and hematocrit average values increased, with wide individual variations. There is no relation between hemopoietic response and duration of the residence at high altitude. Polycythemia is of the normocitic type. There was an increase of lymphocytes and monocytes, and a decrease of neutrophils, without any change in the total number of leucocytes. The sedimentation rate of the red cells decreased.

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Excretion of Neutral 17-Ketosteroids in Human Subjects Repeatedly Exposed to Hypoxia under Conditions of Simulated High Altitude[1]

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INVESTIGATIONS ON EXPERIMENTAL ANIMALS have shown that the adrenal cortex is affected by exposure of the animals to conditions of hypoxia or reduced pressure (1–10). In the human, appraisal of adrenal involvement in the response to similar conditions is complicated by the lack of a definite measure of adrenal function. It is generally assumed that part of the neutral 17-ketosteroids excreted in the urine represent metabolic degradation products of substances produced by the adrenal cortex, and there is some evidence that the quantity of ketosteroids excreted may be roughly proportional to the functional activity of the adrenal cortex (11).

The investigation of ketosteroid excretion reported here was part of an experiment in which several aspects of physiological change at high altitudes were studied. The ketosteroid study was undertaken to determine whether or not the adrenal cortex is involved in the response of the human subject to simulated conditions of high altitude. The other parts of the experiment are reported elsewhere.

PROCEDURE

The subjects of the experiment were medical students, in good general health. Throughout the experiment, including the control periods, the subjects were maintained on a 3-day rotational diet which was considered to be nutritionally adequate and was rigidly supervised. Twenty-four-hour urine specimens were collected with 10 cc. of 10 N H_2SO_4 added as a preservative. Collection bottles were kept in the refrigerator as much of the time as was consistent with total collection and at all times after the daily collection was complete.

Two separate experiments were conducted using 2 different groups of subjects. In the first experiment, *Group I*, the subjects were exposed to a simu-

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lated altitude of 18,000 ft. without oxygen and in the second experiment, *Group II*, to a 35,000-ft. altitude with oxygen. The exposures were carried out 3 times a week in a low-pressure chamber which would accommodate 13 individuals. Each exposure was one hour at the maximum altitude.

Group I. Eleven subjects, aged 20 to 26 years, were placed on the dietary regimen for a control period of 4 weeks. The subjects were then exposed 3 times weekly to a 13,000-ft. altitude without administration of oxygen, for a period of 9 weeks. After the last exposure the subjects were maintained on the dietary regimen for 9 days as an additional control. For convenience in handling the data, the entire term of the experiment has been divided into 5 periods; the pre-exposure period, 3 periods during which the subjects were exposed to the high altitude (*Exper. periods I, II, III*), and a 4th period which is called the post-exposure period although it includes 4 exposures with oxygen inhalation which were followed by 9 days without exposure.

Determinations of the ketosteroids were made on 8 consecutive days during the pre-exposure period and every 3rd day throughout the remainder of the experiment.

Group II. Seven subjects, aged 20 to 26 years, were placed on the dietary regimen for a control period of 12 days (pre-exposure period). During the next 12 days (*Exper. period I*) they were subjected to voluntary hyperventilation on 5 occasions. In the next 12-day period (*Exper. period II*) the subjects were exposed 4 times to a 35,000-ft. altitude with administered oxygen for a total time of 90 minutes plus 50 minutes at 35,000 ft. with oxygen. In the following 14 days (*Exper. period III*) they were exposed 5 times to 35,000 ft. with oxygen for a total exposure time of 5.25 hours. During the last 12 days of the experiment (post-exposure period), the subjects were not exposed, but were maintained on the dietary regimen. Ketosteroid determinations were made daily instead of every 3rd day as in the first experiment.

METHODS OF KETOSTEROID DETERMINATION

The extraction of ketosteroids in the first experiment (*Group I*) was carried out by a modified benzene method. This method, suggested by Drs. F. C. Koch and T. F. Gallagher, was designed to fit the circumstances under which the extractions were made. The dry residues obtained were taken up in 95% ethyl alcohol and determinations of the 17-ketosteroid content were made by the Holtorff-Koch method (12) using m-dinitro benzene as the reagent. Readings were made on a Klett-Summerson photoelectric colorimeter with a 520 $\mu\mu$ green filter using crystalline androsterone[4] as a reference substance. The ketosteroid values were calculated on the basis of 24-hour output.

[4] The crystalline androsterone was kindly furnished by Ciba Pharmaceutical Products, Inc., Summit, N. J.

Correction for the intrinsic color of the extracts was also made according to the method of Holtorff and Koch (12) employing a simultaneous determination of the extract without the reagent. The value obtained with this blank was subtracted from the value for the extract with the reagent. Determinations on each extract without the reagent gave a measure of the intrinsic colored substance presumably not due to the ketosteroids present in the extract. This colored substance or chromogen as it is termed, varied in intensity from light pink to dark red. It appeared on hydrolysis of the urine and persisted throughout the extraction process. The values obtained for the amount of this color have been converted to arbitrary day-units and are thus expressed in the

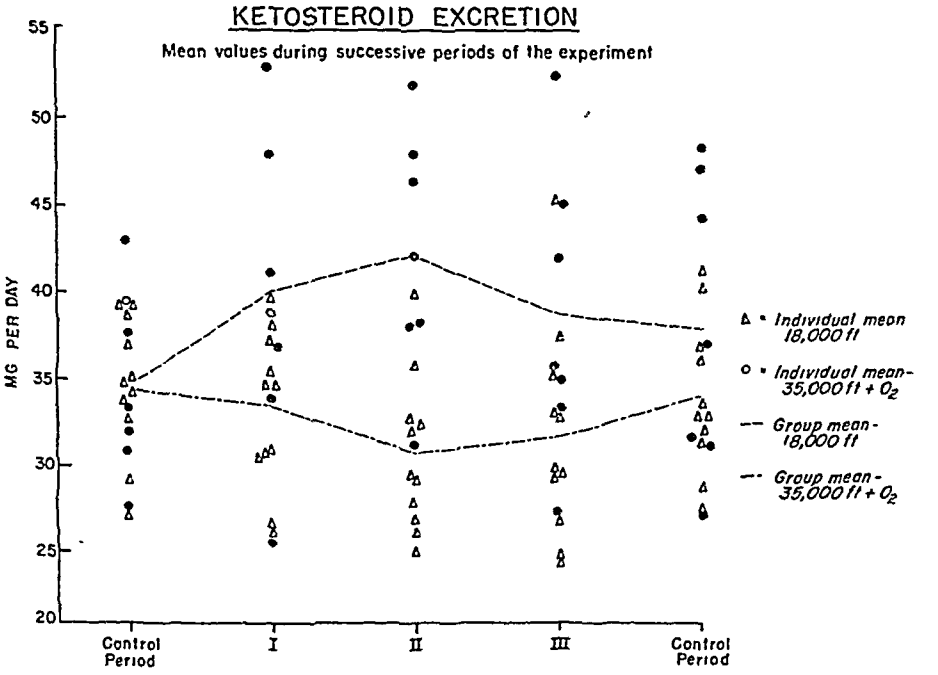

Fig. 1.

graphs. The identity of the substance or substances in the urine which give rise to the color obtained has not been ascertained.

In the second experiment (*Group II*) the extraction method employed was that of Pincus and Pearlman (13), using ether as the extractive. This method was employed because the shorter time involved in the extraction process allowed daily determinations to be done instead of determinations every third day as in the first experiment. Checks on the 2 methods gave comparable results and reference to figure 1 shows that the control values for the 2 groups of subjects fall essentially within the same range. Determinations of the ketosteroids were carried out as for *Group I*.

RESULTS

Group I. Ketosteroids. The ketosteroid values for any subject during the pre-exposure period showed considerable fluctuation. During the periods of exposure to stimulated altitude no immediate effect on the ketosteroid values was observed, i.e. fluctuation in values persisted with no apparent relation to exposure. In order to determine whether or not any general effect on the

TABLE 1. GROUP I. EXPOSURE TO A SIMULATED ALTITUDE OF 18,000 FT. WITHOUT OXYGEN

SUBJECT	PRE-EXPOSURE PERIOD	EXPOSURE PERIODS			POST-EXPOSURE PERIOD
		I	II	III	
		Ketosteroids[1]			
1	37.08	36.80	32.40	26.79	32.67
2	32.71	27.52	28.84	23.93	27.60
3	33.75	30.23	32.09	29.41	33.03
4	38.45	39.67	39.47	32.98	40.95
5	33.61	30.38	29.26	29.26	32.05
6	27.08	34.86	32.25	24.49	31.29
7	29.03	34.77	27.98	34.89	36.59
8	34.96	27.12	26.07	30.17	28.43
9	38.74	35.20	29.10	33.11	36.01
10	38.90	37.85	35.51	46.09	40.31
11	34.75	30.48	26.78	37.24	32.55
Means	34.46	33.17	30.52	31.67	33.77
		Chromogens[2]			
1	0.1	2.9	3.4	1.4	0.2
2	3.1	16.0	12.0	6.2	8.6
3	0.8	4.9	4.3	1.9	1.0
4	7.5	25.2	23.2	21.5	33.6
5	4.3	23.0	15.2	13.7	17.5
6	4.3	1.7	1.3	0.6	0.0
7	3.7	12.3	10.2	12.5	15.3
9	6.0	10.0	6.9	11.1	9.3
10	0.9	7.5	9.0	20.8	17.5
11	4.4	4.4	3.3	4.3	2.0
Means	3.7	11.3	9.5	10.6	10.8

[1] Mean values are expressed in mg/day. [2] Mean values are expressed in units/day.

level of ketosteroid excretion was being produced by continued exposure, the data were arranged so as to compare the mean values for each individual during successive periods of exposure to the pre-exposure mean for that individual. Table 1 shows the values thus obtained for each individual. In figure 1 these values have been plotted in the form of a scattergraph.

It is apparent from the values in table 1 that, in general, no marked

changes in the ketosteroid levels occurred throughout the experiment. However, statistical analysis of the group means showed a significant decrease from the control mean during the second exposure period (C.R. 2.26). Examination of the individual curves based on mean values for successive periods of the experiment showed, in most individuals, a decrease in ketosteroid level during the first 2 or 3 periods of exposure. This tendency of the group in general is reflected in the graph (fig. 1) which shows the individual means as well as the group mean for each period. The general shape of the mean curve for the group leads to the following interpretation: throughout the first 2 periods of intermittent exposure to 18,000 ft. there was a lowering of the ketosteroid

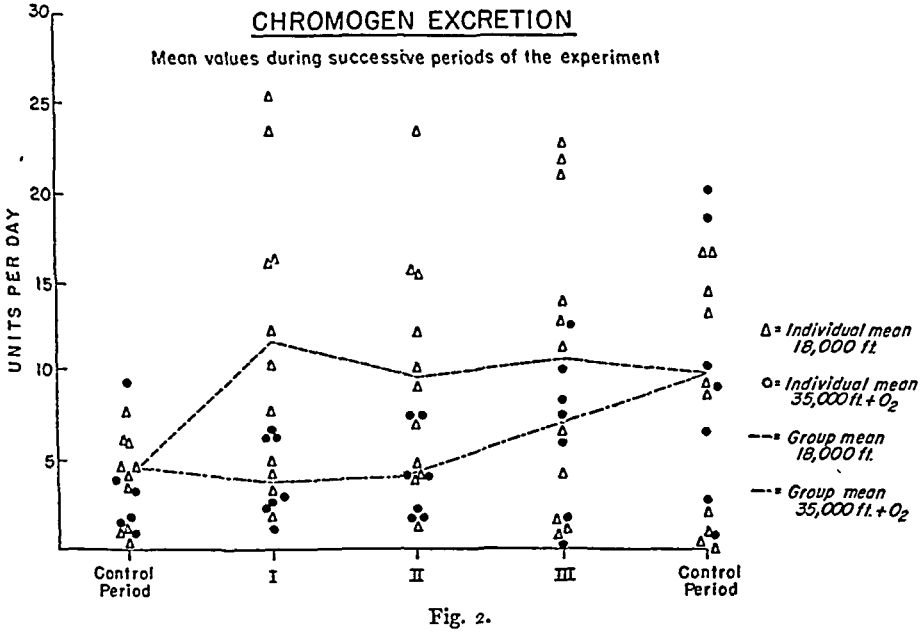

Fig. 2.

excretion level, but during the third period of exposure a reverse trend toward the pre-exposure level occurred; this occurred at the time when the ascorbic plasma level was the lowest. There was an almost complete return to the original level during the final period (post-exposure period).

Chromogens. The substance or substances responsible for development of the intrinsic red color in the extracts (cf. METHODS OF KETOSTEROID DETERMINATION) also showed considerable fluctuation in quantity on successive determinations. However, the chromogen data, when handled in the same way as the ketosteroid data (fig. 2) showed, for most individuals, a marked increase in the mean output during the first exposure period. The group mean for this period was significantly greater than the pre-exposure mean (C.R. 3.04).

This general increase in chromogens was maintained throughout the ex-

periment, although in some individuals there was a tendency to return toward the pre-exposure level during the final period of the experiment. One individual showed a remarkably high chromogen mean during this final period (fig. 2). If the value for this individual is excluded from the group mean, the tendency to return to the pre-exposure level becomes more apparent.

Group II. Ketosteroids. The ketosteroid excretion for the individual subjects in this experiment also showed considerable daily fluctuation. However, when the data was handled as in *Group I*, using mean values for successive

TABLE 2. GROUP II. EXPOSURE TO A SIMULATED ALTITUDE OF 35,000 FT. WITH OXYGEN

SUBJECT	PRE-EXPOSURE PERIOD	EXPOSURE PERIODS			POST-EXPOSURE PERIOD
		I[1]	II	III	
		Ketosteroids[2]			
1	42.72	52.48	51.58	52.23	47.14
2	33.14	38.50	41.73	35.27	31.11
3	32.06	36.62	37.75	33.28	36.96
4	30.70	33.87	37.79	34.69	31.34
5	27.38	26.65	31.34	27.63	27.17
6	37.53	47.65	46.12	46.00	47.80
7	39.34	41.21	47.48	41.42	44.03
Means	34.70	39.57	41.97	38.65	37.94
		Chromogens[3]			
1	0.4	0.8	1.4	0.3	1.8
2	13.0	6.3	7.4	10.1	10.3
3	3.0	2.8	3.7	12.2	21.1
4	9.3	6.3	7.5	7.5	19.6
5	1.0	2.6	1.6	1.6	2.5
6	4.0	2.3	2.1	5.7	6.6
7	1.6	6.6	3.8	8.3	9.0
Means	4.6	4.0	5.9	6.5	10.1

[1] Hyperventilation period. [2] Mean values are expressed in gm/day. [3] Mean values are expressed in units/day.

periods of the experiment, a progressive change in the ketosteroid excretion was observed. This change was the reverse of that noted in *Experiment A*, i.e. the ketosteroids were increased in quantity rather than decreased. This group manifested a hyperexcretion of ascorbic acid. Table 2 and figure 2 show the general tendency toward increased ketosteroid excretion during the period of hyperventilation (*I*) and the following period of intermittent exposure to a 35,000-ft. altitude (*II*). Although the increases above the pre-exposure mean were not statistically significant, the individual curves show a general consistency in the type of response which might be considered to offset somewhat

the statistically insignificant degree of change. During the third experimental period (*III*), while exposure was continued, and during the post-exposure period there was a general tendency toward a return to the control level.

Chromogens. As in *Group I*, the chromogen values for each individual in this group showed daily fluctuations. However, the pre-exposure mean of the group was very close to that of *Group I* (fig. 2). No change in chromogen excretion occurred during hyperventilation at ground level, although an increase appeared later on exposure to 35,000-ft. altitude with oxygen. The change, however, was delayed until the second period of actual exposure (*period III*). This delay is thought to be due to the fact that the total exposure during the first period was only 140 minutes. The effect, therefore, became apparent when the total exposure time was increased (5¼ hr.). The chromogen mean of the group was still further increased during the post-exposure period. This further increase, however, was due to the high values obtained for 2 of the 7 individuals.

DISCUSSION

The results show a tendency toward a decrease in ketosteroid excretion with intermittent exposure to 18,000 ft. without oxygen and a tendency toward an increase with exposure to 35,000 ft. with oxygen. In both cases these effects were only temporary since continued exposure tended to be accompanied by a return toward pre-exposure levels. This suggests the operation of an adaptive mechanism such as has been observed in animal experiments (6, 7 and 9).

The question arises whether or not the depression in ketosteroid excretion which occurred with exposure to 18,000 ft. was due to oxygen want. At the higher altitude with administered oxygen and a hyperexcretion of ascorbic acid, there was no depression in ketosteroid excretion; rather there was a slight but consistent elevation. An elevation in steroid excretion also occurred with hyperventilation at ground level. Since there was undoubtedly hyperventilation in association with the exposure to 18,000 ft., it seems reasonable that the decrease in ketosteroid excretion at this altitude may have been caused directly by the hypoxia. It was associated with a decrease in the urinary excretion and plasma level of ascorbic acid.

Neufeld (14) has reported that the ketosteroid excretion of rats is markedly decreased by exposure to high altitude. The depression in the ketosteroid excretion of human subjects on exposure to high altitude without oxygen is therefore consistent with the findings in the experimental animal. The lesser degree of change noted in the human subjects may be due to the fact that comparatively less drastic conditions of exposure were employed than in the animal experiments.

The 17-ketosteroids in the urine supposedly represent not only products of adrenal steroid metabolism, but also metabolically transformed testicular steroids. Fraser, Forbes *et al.* (11) have found that in patients with Addison's

disease the ketosteroid excretion is markedly reduced. In females with this disease they found no ketosteroids, while in males some ketosteroids were found but the level was very low. This residual ketosteroid excretion in males with hypo-functioning adrenals they consider as representing that fraction which is derived from the testicular secretions. In view of this, it is necessary to postulate that the decrease in excretion of ketosteroids found with exposure to altitude (18,000 ft.) may reflect a depression in testicular function rather than an alteration in adrenal-cortical function. Recent work on the rat (15) presents evidence that exposure to high altitude causes reduction in the weights of the testes, prostate and seminal vesicles, indicating a probable diminution in androgen production by the testes.

Because of lack of information concerning the nature of the chromogenic substance found in the urine, the significance of an increased excretion of this substance caused by exposure to high altitude cannot be surmised. Some random experiments indicate that perhaps the chromogenic substance and the ketosteroids are somehow related since efforts to increase or decrease the one by artificial means have generally caused a concomitant increase or decrease in the other.

SUMMARY

Two groups of human subjects on a controlled diet were intermittently exposed to simulated high altitudes. The first group (11 subjects) was exposed to 18,000 ft. without oxygen; the second group (7 subjects) was subjected first to a series of hyperventilations at ground level and then exposed to 35,000-ft. altitude with oxygen. Determinations of the neutral 17-ketosteroids and of chromogens were made on the urine of all subjects during the exposure periods and during the control periods at the beginning and end of each experiment. During intermittent exposure to 18,000 ft. without oxygen ketosteroid excretion was at first decreased, but as exposure was continued it returned to the original control level. Upon hyperventilation the ketosteroid excretion tended to be increased. Intermittent exposure to 35,000 ft. with oxygen also caused a temporary increase in ketosteroid excretion followed by a return toward the control level. However, the post-exposure level was higher than the pre-exposure level. This suggests that the effect of oxygen inhalation on 17-ketosteroid excretion should be studied further. Excretion of the chromogenic substance or substances, the nature of which is unknown, was increased by exposure to high altitude, but was not altered by hyperventilation at ground level. The results show that some alteration in ketosteroid excretion occurs in the response of the human subject to conditions of simulated altitude. These results alone, however, cannot be considered proof that the adrenal cortex is functionally involved in this response.

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Influence of Bimanual Exercise on Unilateral Work Capacity[1]

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WORK DONE PREVIOUSLY in this laboratory (1) had demonstrated that unilateral progressive resistance exercise which rapidly augments the strength and endurance of the homolateral limb, has a strikingly similar concurrent effect on the unexercised contralateral extremity. The phenomenon had been discussed originally in the psychological literature of the late 19th and early 20th century (2–6). Cross education was demonstrable only when the subject was sufficiently cooperative and trained to put forth an all-out effort which approximated in its severity the maximal physiological work attainable under the conditions imposed. It was postulated that widespread synergistic cocontractions, manifest as variations in muscle tone and attitude essential to the preservation of balance, were responsible for the phenomenon. The present study is an extension of the observations made in 1947.

When loss of strength and endurance is the primary cause of physical disability, the restoration of function is dependent upon the ability of the patient to exercise systematically in the over-load zone. The amount of work done per unit of time is of critical importance, and unless this exceeds that which can be done easily, little progress is made in the restoration of strength. Voluntary cooperation of the patient is imperative. Since nociceptive impulses emanating from traumatized tissues, fear of pain, deliberate or unconscious malingering mitigate against successful treatment, the finding of ways and means of expediting work capacity stands as a problem of first importance to the successful rehabilitation of the disabled suffering from disorders of the neuromuscular and skeletal systems. The purpose of this paper is to evaluate a simple, reflex method of augmenting work output.

METHODS

If vigorous unilateral exercise elicits associated movements or increased tone in symmetrically disposed muscle groups, it was postulated that the concurrent contraction of homologous parts might be sufficiently dynamogenic to

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excite the weaker side to increased effort. Most human subjects demonstrate the phenomenon of laterality. Thus, the normal individual manifests a physiological difference in the functional capacity of symmetrical structures not unlike that present in the disabled except in degree. Selected muscle groups of the right and left upper extremity were subjected alternately to identical stress until the weaker of the two sides failed to accomplish the requisite number of contractions against a prescribed load in the assigned rhythm. The dominant limb was then made to contract synchronously with the one which had failed. The object of the experiment was to study the influence of bimanual exercise on the work capacity of the weaker extremity.

The subjects of the experiment were 29 normal healthy adults. They performed 52 experiments consisting of 962 unilateral and 268 bilateral exercise bouts. Nine were excluded subsequently because cessation of exercise occurred without adequate evidence of fatigue. Few untrained subjects are inured sufficiently to the discomforts of severe exercise to put forth a reliable all-out effort unless strongly motivated to do so. A mean decrement of at least 30 per cent in work output per bout was accepted as the most unbiased criterion of adequate performance. Variations in the duration of exercise were thus also equalized. This left a group of 32 experiments performed by 20 subjects, 5 male and 15 female, varying greatly in strength.

Work was done on two nearly identical ergographs (7) and consisted of maximal volitional wrist extension. Slight differences in friction and weight of the load carriage of the two ergographs were disregarded. Whatever advantage they gave was in favor of the weaker side of the average subject. Shen (8) has shown that equally heavy weights simultaneously lifted are far from psychologically equally heavy. When the equipment was loaded under experimental conditions, the relative magnitude of the difference diminished and probably fell to a point significantly below the threshold of bilateral discrimination.

The load selected was lifted and lowered repetitively to the rhythm of an audio-visual metronome set at 100. The work was performed as a two-count exercise without pause at the peak of the shortening or termination of the lengthening phase of each movement cycle. Each extremity performed 25 repetitive contractions unilaterally, commencing with the preferred hand. The contralateral limb remained at rest during the exercise of the opposite extremity. Thus every 30-second period of exercise was followed by a 30-second rest pause. The subjects were urged to make every contraction a maximal volitional effort. Inspection of the ergograms indicated whether or not performance was reliable. Two experiments were excluded because the range of movement fell off precipitously, and was then maintained at partial extension for a protracted interval of time without appreciable reduction. When the load could no longer be lifted the requisite number of times in the prescribed rhythm, the standard rest pause of 30 seconds was allowed after which both hands exercised concurrently. The relation of the work done in the last unilateral bout

of the failing side to the functional capacity in the first bilateral bout was accepted as the criterion in terms of which the dynamogenic effect of the procedure might be judged.

The single most difficult step in the procedure was to arrive at a reliable method of selecting a load which would produce progressive fatigue at a rate rapid enough to prevent invalidating errors in work capacity, due to stereo-

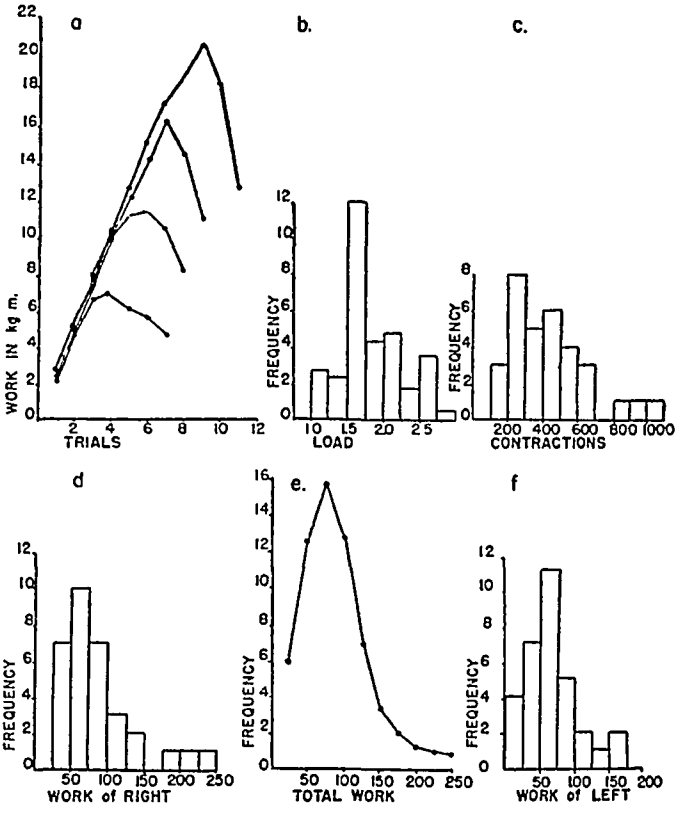

Fig. 1. *a*) CURVES OF WORK illustrating response of subjects of varying strength to successive bouts of 25 repetitive contractions/30-sec. lifting loads which increase by increments of .25 kg. *b*) Frequency distribution of load carried during exercise. *c*) Frequency distribution of total no. of contractions prior to failure of the weaker hand. This indicates the range and variability of the duration of the total effort. *d*) Frequency distribution of work done by the right hand prior to the failing bout. *e*) Smoothed frequency histogram of total work done prior to the failing bout by the right and left hands combined in alternate bouts of 25 repetitive contractions each. *f*) Frequency histogram of work done by the left hand prior to the failing bout.

typing and boredom, but not so rapidly that the load could no longer be lifted after 40 or 50 contractions. Preliminary trial suggested 8 bouts or 200 contractions per extremity as the optimal stress for the purposes of the experiment. The load was selected by the so-called limit-day procedure (9). This was administered to the nonpreferred and presumably weaker hand. The rhythm and number of contractions per bout were held constant. The load was the independent variable. In the majority of experiments this commenced with .25 kg.

and increased by equal increments in successive bouts until the speed and duration constants could no longer be met. The standard rest pause was interposed between bouts. The curve of work for each subject was then computed. These vary with the strength of the subject, but are strikingly similar (fig. 1) if the experiment is well performed and every contraction is an all-out effort.

If the limit day test has been reliably administered, any load beyond the intra-individual optimum will be fatigue-producing. The further it falls in the over-load zone the more rapid will be the exhaustion. Thus in approximately 50 per cent of the cases, the load selected was that carried in the bout which preceded the one in which the subject failed to execute the assigned number of contractions. In the remaining cases it was either reduced or increased, depending upon the shape of the curve of work, the behavior of the subject, and the slope gradient of the ergographic fatigue curve. Although the ergograms are highly diagnostic to the experienced observer, cues inherent in the records were obviously misjudged in the early phases of the experiment. The inclusion of subjects who had performed poorly under the limit day procedure was the most frequent cause for the subsequent elimination of experiments. Errors in gauging a fatigue-producing load were sometimes corrected by augmenting the stress during the subsequent experiment, but this was not always successful. Figure 1 summarizes the range and incidence of the loads carried, the number of contractions and the work done.

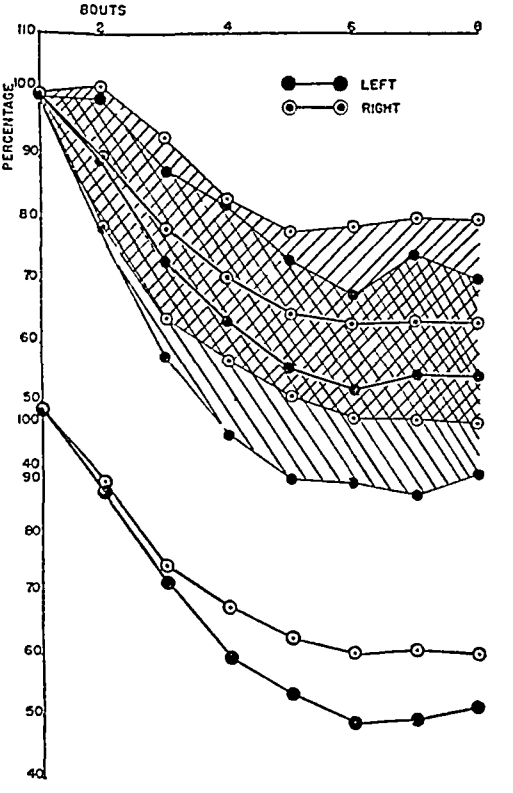

Fig. 2. *a*) (*Upper*) MEAN FATIGUE CURVE of total group. The work done in successive bouts is computed as percentage of initial functional capacity. Shaded areas indicate standard deviation of each mean. *b*) (*Lower*) Mean fatigue curve of the experiments retained after the exclusion of all procedures in which the average decrement in work output/bout was less than 30 per cent.

The mean fatigue curve for the total group and its variability are recorded in figure 2*a*. That for the group retained (fig. 2*b*) indicates that the mean decrement in work capacity prior to bilateral exercise was approximately

40 and 50 per cent for the right and left hands respectively. This was attained on an average in the fifth bout after which steady-state work supervened. Under mounting stress differences in work capacity due to laterality dominance became increasingly evident.

RESULTS AND INTERPRETATION

Comparison of the total work done in the failing bout with that achieved during the cocontraction of the dominant hand indicates that bimanual exercise was significantly dynamogenic. Since the mean number of contractions in the failing bout was usually about 80 per cent of the standard, whereas that of the first bilateral bout was virtually 100 per cent, the statistical significance of the effect was also computed on the basis of the work done per stroke. The results are summarized in table 1. The evidence indicates that the revival in strength evoked by bilateral exercise was not only conducive to augmentation in endurance, but also enhanced contractile power.

TABLE 1. INFLUENCE OF BIMANUAL EXERCISE ON UNILATERAL WORK CAPACITY

LAST UNILATERAL BOUT		FIRST BILATERAL BOUT		DIFF.	S.D. OF DIFFERENCE	C.R.
MEAN	S.D.	MEAN	S.D.			
kg.m.		*kg.m.*		*kg.m.*		
Total Work Done by the Failing Hand						
4.45	1.87	6.16	2.32	1.71	.53	3.23
Work Done per Stroke by the Failing Hand						
0.229	.0251	0.257	.0289	0.0284	.0068	4.18

Figure 3 illustrates the revival in strength demonstrated by a well trained subject. Figure 4 contains other examples. The mechanism of the effect may be psychogenic, or explainable in terms of facilitating irradiation of motor impulses when exercise is carried on under conditions of maximal voluntary innervation. In 1934 Metfessal and Warren (10) observed overcompensation by the non-preferred extremity of right and left handed subjects when the first two fingers of both hands were moved simultaneously. Action potentials appeared first in the hand not used in writing.

Revival in strength also occurred on the dominant side. This is well illustrated in figure 3. The magnitude of the revival was not computed because the rest pause preceding sychronous bilateral activity was equal to 30 seconds plus the period during which the contralateral limb was executing the failing bout. Since the effect of the added rest *per se* was unknown, quantitative study of the improvement in work capacity would have little meaning. However, it was observed that the subjects had a tendency to throw the stronger hand upward during bimanual activity, as though the preferred limb was uncon-

sciously exerting more force than previously. The load carried by the dominant hand felt curiously light when lifted in synchronous rhythm with the opposite extremity.

In 1923 Walshe (11) demonstrated that forceful tonic contraction of the normal arm of patients suffering from hemiplegia evoked associated move-

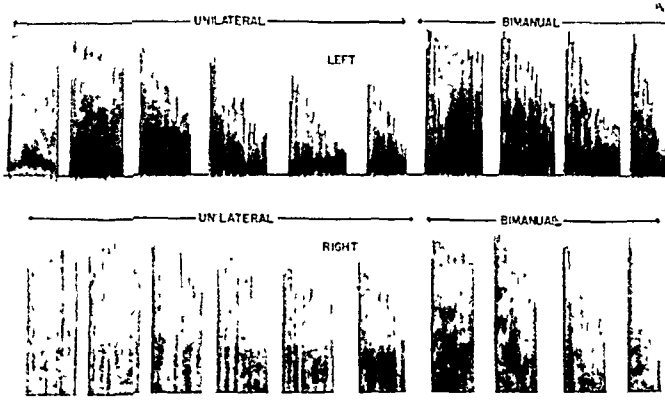

Fig. 3. BILATERAL ERGOGRAMS illustrating fatigue of the dominant and nonpreferred hands when subjected to alternate bouts of repetitive contractions with load, rhythm and rest pauses held constant Revival in strength evoked by contracting both hands simultaneously is also illustrated.

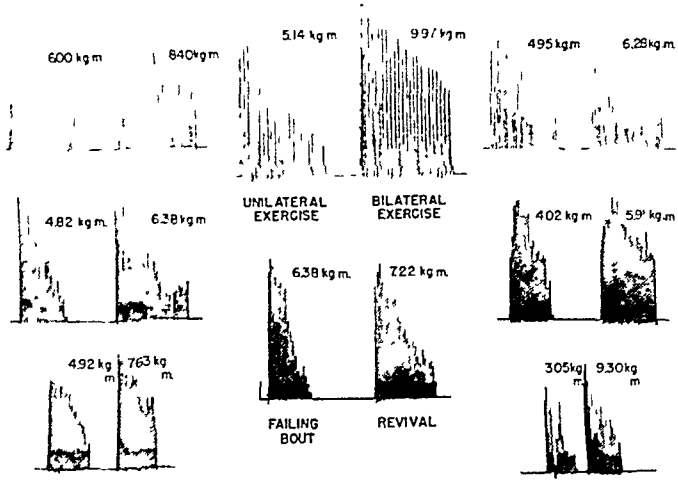

FIG. 4. ILLUSTRATIVE ERGOGRAMS showing last unilateral bout of the failing hand and the revival on the first bimanual bout.

ments in the paralyzed contralateral extremity. In some pathological conditions the movements of the two hands cannot be dissociated. Thus, the child with infantile spastic hemiplegia often demonstrates so-called 'copying,' the involved side executing movements in unison with the normal extremity although powerless to initiate these volitionally. Synkinetic movements of many types may be evoked in the cerebral palsied, many of whom also show facilitation

associated with contralateral inhibition in response to the tonic neck reflex. In our own normal cases we observed repeatedly an unconscious, forceful turning of the head toward the exercising limb concomitant with each contraction, reversing in direction as the bouts shifted from one to the opposite side. Bilateral exercise was associated with hyperextension of the head. Thus there are many reasons to suppose that the dynamogenic effect of the procedure under study is reflex in origin.

Preliminary clinical application of bimanual exercise tends to confirm its probable therapeutic utility. We have observed striking duplication of the exact pattern of contraction by a patient with spastic quadriplegia when made to exercise bimanually. Bilateral work done on the grip ergograph (12), by a patient suspected of malingering, demonstrated that the force of the contraction on the involved side superseded that attained unilaterally, when attention was focused on the activity of the normal extremity. The problems, aroused in differentiating between the psychogenic and neurogenic hypotheses presented, have led to the initiation of further observations on unilateral, bilateral, alternating and reciprocal exercise.

SUMMARY

Return of normal neuromuscular function following injury or disease may be dependent on volitional exercise. If augmentation in strength is the major therapeutic objective the exercise prescribed must be in the over-load zone. Since the will to work at levels which exceed easy performance may be defective, it is sometimes of practical importance to find ways and means of expediting work output reflexly. Thirty-two experiments were made with 20 normal adult subjects to observe the effect of bimanual exercise on the functional capacity of the weaker limb. Cocontraction of the dominant hand indicates that bilateral exercise is significantly dynamogenic, increasing contractile power and endurance.

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Carbon Dioxide Equilibration in the Lung and its Application to the Determination of Cardiac Output[1]

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FICK'S PRINCIPLE was elucidated in 1870 (1), but it was many years before it was applied to man. Now samples of mixed venous blood from the pulmonary circulation are compared commonly with those obtained from a systemic artery to allow routine applications of the principle. Owing to the temporary instabilities in balance, which beset carbon dioxide exchange, the principle has been applied mainly to oxygen utilization. Yet the method has limitations, since numerous repeated observations on a single individual are not practicable.

Many methods have been devised as substitutes, including the dilution effects produced by the circulating blood on injected dye or saline, recoil phenomena associated with cardiac contraction, as well as deductions from observed changes in the size of the heart or from the pressure fluctuations in the large arteries. Indirect applications of the Fick principle have also been made utilizing carbon dioxide, oxygen or a foreign gas, in which the gas contents of venous and arterial blood have been predicted from the gas tensions in the lungs. Such application of the Fick principle in the case of carbon dioxide are of importance as the foundation of the present method and they alone will be discussed here.

For such indirect estimates carbon dioxide is preferable to oxygen, in spite of the difficulties resulting from instability. The method cannot readily be applied to oxygen owing to the low concentrations of oxygen that have to be used, which induce anoxia and are liable to cause mental confusion. Difficulties arise also with foreign gases but these cannot be discussed here.

In the indirect application of the Fick principle, the assumption is made that, if a gas mixture when taken into the lungs neither gains nor loses carbon dioxide, the tension of this gas in the lungs must equal that in mixed venous blood. If the composition of the blood is adequately known, as far as acid-base

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buffers and hemoglobin concentration are concerned, the carbon dioxide tension allows the content to be predicted. The content of this gas in arterial blood can be determined by direct sampling or can be predicted from the tension of arterial alveolar air. In the past 'virtual venous alveolar air' has commonly been employed in determining the content of venous blood, and this precedent has been followed here. Under these conditions a high oxygen content is used in the inspired gas, so that the carbon dioxide tension determined for venous blood is that which exists in blood which is fully oxygenated, but which has been unable to lose appreciable quantities of carbon dioxide.

Such methods have been repeatedly attempted and found inadequate and abandoned, so that it is necessary to explain why any new attempt was made. In the past, starting with Krogh and Lindhard (2), Douglas and Haldane (3, 4), Henderson and Prince (5), and continuing in many subsequent researches, great differences were found in the apparent quantity or quality of venous return according to the method used for obtaining uniform gas mixture in the lungs. Thus Douglas and Haldane found an apparent very low tension in mixed venous blood (3) when the breath was held, while much higher values were obtained with deep breathing (4). Krogh and Lindhard recognized that breathing procedures modified the absolute flow of blood, but neither they nor most of the later workers considered that serious alterations in the composition of mixed venous blood could be caused thereby. All the methods employed active cooperation of the individual under examination with modification of his existing respiratory pattern.

The use of such procedures for obtaining full mixing of gases in the lungs seemed both justifiable and essential at that date. Now they are no longer justifiable. It has been shown by Shore *et al.* (6) that the composition of the blood in the superior and inferior venae cavae in dogs differs greatly. The same must be true in man. It is now known that the cerebral return constitutes a large proportion of the resting blood flow in the superior vena cava. Since this cerebral blood has an unsaturation of approximately 60 ml. of oxygen per liter, the blood in the superior cava must be relatively highly unsaturated. On the other hand the larger proportion of the blood in the inferior cava is derived from the liver (with an oxygen unsaturation of only some 35 ml/l.) and the kidney (with one of only some 10 ml/l.); its oxygen unsaturation must therefore be low. It is inconceivable that respiratory movements could be greatly modified without temporarily altering the ratio of these two inflows to one another, thus modifying the composition of the pulmonary blood. The present method differs from its predecessors in insisting on a maintenance of a normal respiratory pattern.

The possibility of errors arising, if the respiratory pattern is altered, cannot be denied. However the importance of such errors is not established. One might anticipate that holding the breath in an inspiratory position might modify the

situation, but it is not clear why taking repeated deep breaths should apparently alter the composition in the opposite direction; yet relatively low arteriovenous carbon dioxide differences have been usually reported with breath holding, and much higher values with forced deep breathing. It is quite possible that more than one source of error exists, and that errors of opposite sign sometimes may counteract each other. Since a short temporary vasoconstriction in the finger vessels can be demonstrated to result from a voluntary deep inspiration (7), the possibility of similar reactions in less accessible vessels cannot be excluded. Such a vasoconstriction occurring in the renal vessels could not be demonstrated readily with present technics, but it would greatly alter the composition of mixed venous blood. That opposing mechanical and reflex factors may be concerned in causing errors is suggested by the interesting work of Gray, Bing and Vandam (8) which to some extent stimulated this research. With a routine combining deep breathing and breath holding, credible values for the carbon dioxide tension of mixed venous blood were often obtained, but the consistency was not high. Other evidence suggesting the possibility of errors from changed respiratory patterns is given in results obtained following exercise. Under these conditions respiration is very active and cannot easily be modified. The old indirect estimates from carbon dioxide exchange gave values which agree (for similar levels of oxygen consumption) closely with recent estimates made after exercise by the direct Fick procedure. For this observation we are indebted to a personal communication from Dr. C. G. Douglas to one of us (*H. C. B.*).

The problem of utilizing carbon dioxide exchange for the measurement of cardiac output depends on three factors: *1*) the introduction of a gas with a proper composition into the lung and the production of adequate mixing within a period of 15 or at most 20 seconds without voluntary modification of the respiratory pattern or other cooperation by the subject; *2*) the use of adequate precautions to ensure a stable balance in carbon dioxide exchange at the time of measurement; *3*) the utilization of the determined gas tensions to determine the actual composition of mixed venous blood. The present paper is concerned mainly with the practicability of the first of these; the second and third factors are scheduled for later investigation.

The conclusion could readily be drawn from past literature that adequate mixture of gases in the lung is not a possibility within 15 seconds with quiet respiration. This conclusion is not valid. Mixing in the whole respiratory path may be slow but the main difficulty arises from the dead space; in any case mixing in the alveoli is by no means as difficult as was assumed by the earlier workers. They found that breathing deeply gave an apparent equilibrium at a level different from that obtained with shallower breaths. They therefore thought that adequate mixing had not occurred in the latter case. Only Douglas and Haldane paid attention to the possibility of altering the ratios of the

blood stream returning from different areas. Even they did not credit such a factor as possibly causing unwarranted conclusions on gas mixtures. The older data on mixing in the lungs cannot therefore be accepted as necessarily valid.

METHODS

Rapid mixing of gas in the lungs was at first attempted by modifications of the two-bag system recommended by Gladstone (9). Later rebreathing from a single bag was utilized, but the difficulty of obtaining an initial rapid rise in the alveolar carbon dioxide tension was overcome by enrichment of the first inhalation with a measured additional volume of pure carbon dioxide. This enabled equilibrium to be approached rapidly without later respirations introducing excessive amounts of carbon dioxide. The amount of gas so added to the first inspiration was calculated according to the principles discussed later.

All the determinations were made on three experienced subjects, whose weights, heights and estimated surface areas are given in table 1. Through the courtesy of Dr. W. F. Fowler of the Department of Physiology in the Graduate School of Medicine the functional residual airs (that amount of air present in the lungs at the end of a normal expiration) were determined in each subject by the Darling (10) method. Though these determinations were not essential for the method, they helped to establish factors that are probably concerned. Values for three subjects are also given in table 1. The subjects were basal, and examinations were made after 45 to 60 minutes recumbency in a room at 22°C. (usually with about 50% humidity). The experiments here reported were carried out in the spring (see table 1), so that the subjects were not exposed to extreme climatic conditions before entering the room. The usual routine was as follows: *a*) Haldane Priestley expiratory alveolar air sample; *b*) two complete rebreathing procedures; *c*) determination of the output of carbon dioxide by spirometry; following this *b*) was repeated and then *a*). Ten minutes was allowed for recovery after any alveolar air procedure, whether arterial or venous. It is reasonable to suppose that the means of the alveolar air samples symmetrically spaced on either side of the carbon dioxide output measurement corresponded with this output.

The equipment used is as follows. A mouthpiece of soft rubber connected the subject with a slide valve, and his nose was closed with a light clip. The slide valve was constructed of lucite and plexi glass, equipped with three ports. The inspiratory and expiratory ports were fitted with Japanese gas-type (11.1) valves (obtained from Warren G. Collins Company, Boston, Mass.). These provided low resistance and volume of dead space. The inspiratory port could be left open to air, or attached to an O_2 supply. The expiratory port was connected to a spirometer.

The valve could be easily slipped to the third port. This was equipped

with a 1500 cc. rubber bag for rebreathing, or a 5-foot rubber hose for the expiratory alveolar airs. Samples were taken at the level of the teeth by a small rubber catheter (i.d. = 0.15 cm.) in the mouthpiece. The total dead space of this port from mouthpiece to mouth of bag was 26 cc. In its base the third port had a small bag sampling tube and a large (i.d. = 0.6 cm.) tube slanted toward the mouthpiece. The large tube permitted the addition of a measured volume of 100 per cent CO_2 to the first inhalation of the rebreathing procedure.

The bag volume was kept at a minimum so that by 20 to 25 seconds the subject would be emptying the bag but would not be deprived of air. The mixture used in the bag consisted of CO_2 6 per cent; O_2 34 per cent and N_2 60 per cent.

In the rebreathing procedure, after the valve was moved to the third port and the 100 per cent CO_2 added to the first breath, end expiratory samples of most or all respirations were taken for the first 30 seconds. Sampling tubes (11) were especially constructed to clear the dead space of the sampling catheter before each sample was taken. Analyses were done on a Scholander apparatus so that sample volumes were only 5 to 10 cc., enabling us to avoid reducing lung-bag volumes greatly. Timing of the samples was by stopwatch.

The volume of carbon dioxide to be added to the first inspiration depends on the level to which the total gas mixture has to be raised to attain equilibrium, and the volume of gas involved. For this reason the data of the functional residual airs are useful. Actually in the absence of this information one or two preliminary experiments can decide the magnitude of the amount needed to provide a 'plateau' within a requisite short period of rebreathing. For instance suppose that the arterial alveolar concentration of carbon dioxide was 5.5 per cent and the point of equilibrium was of the order of 7.0 per cent in *subject C.W.* If the volume of the bag and its accessories was 1000 ml. and the gas was 6 per cent CO_2, the amount of extra carbon dioxide needed to reach equilibrium is 0.015 (2450) for the alveolar gases and 0.01 $\times$ 1000 for the bag or a total of 37 + 10 or 47 ml. If the initial carbon dioxide added was 43 ml. (as is indicated to be the most suitable volume for this subject according to fig. 1) the total amount to be added by the lungs would be only 4 ml. One might imagine that much larger amounts could be added readily by a system producing normally some 3 ml. per second, but this is not the case, since the conditions of equilibrium must be approached and at equilibrium the output is nil. Actual estimates were made by spirometry to determine the approximate output of carbon dioxide per second, when the subject inspires a 6 per cent concentration of carbon dioxide in oxygen. The rate of output in four experiments on two subjects fell in the range of 0.3 to 0.5 ml. per second for durations such as those employed in rebreathing.

TABLE 1. CARBON DIOXIDE EQUILIBRIUM VALUES AND DERIVED CARDIAC OUTPUT VALUES

DATE 1949	PULSE RATE	CO_2 OUTPUT/MIN.	AV. ALVEOLAR CO_2 TENSION	VIRTUAL VENOUS CO_2 TENSION	CO_2 A-V DIFFERENCE	CARDIAC OUTPUT	STROKE VOLUME
	mm.$^{-1}$	*cc.*	*mm. Hg*	*mm. Hg*	*vol. %*	*l.*	*ml.*
C. W.	(*Ht. 70 in., Wt. 169 lb., S. A. 1.92M*^{2}, *Functional Residual 2450 cc.*)						
A 4/27	57	181.5	38.3	49.1	4.8	3.78	66.3
5/5	57	175.8	39.6	47.44	3.52	5.00	87.9
	58			49.82	4.40	4.0	69.0
5/13	56	170.6	40.54	48.59	3.50	4.88	87.1
	56			50.87	4.35	3.97	71.0
Mean	56.8				4.11	4.33	76.26
Median	57.0				4.35	4.00	71.0
B 4/27	60	181.5	38.3	51.0	5.53	3.28	54.8
5/2	56	181.5	40.15	51.05	4.6	3.95	70.6
				48.97	3.82	4.76	85.0
5/5	54	175.8	39.6	49.45	4.26	4.13	76.5
	53			48.51	3.92	4.49	84.8
				49.0	4.1	4.29	81.0
Mean	55.6				4.37	4.15	75.4
Median	55.0				4.18	4.21	78.7

DATE 1949	PULSE RATE	CO_2 OUTPUT/MIN.	AV. ALVEOLAR CO_2 TENSION	VIRTUAL VENOUS CO_2 TENSION	CO_2 A-V DIFFERENCE	CARDIAC OUTPUT	STROKE VOLUME
	mm.$^{-1}$	*cc.*	*mm. Hg*	*mm. Hg*	*vol. %*	*l.*	*ml.*
C. J. M.	(*Ht. 68.5 in., Wt. 157 lb., S.A. 1.86M*^{2}, *Functional Residual Air 1970 cc.*)						
A 5/6	48	180.5	41.70	51.10	3.86	4.68	97.5
5/16	62	185.1	42.46	49.82	3.06	6.05	97.6
	68			49.70	3.01	6.15	90.5
5/20	72	202	44.36	50.62	2.5	8.08	111.2
	74			51.00	2.63	7.68	103.7
5/30	60	196.2	42.09	52.43	4.2	4.67	77.8
Mean	64				3.21	6.21	96.4
Median	65				3.04	6.10	97.6
B 5/6	48	180.5	41.7	49.9	3.43	5.26	109.5
5/9	56	180.5	42.04	50.96	3.66	4.93	88.0
5/18	68	186.0	41.42	50.3	3.70	5.03	74.0
5/20	78	202.0	44.36	51.14	2.68	7.54	95.7
	69			52.14	3.05	6.62	96.0
5/23	64	184.8	43.40	51.3	3.16	5.85	91.0
5/30	60	196.2	42.09	50.7	3.55	5.53	92.2
Mean	63.3				3.32	5.82	92.3
Median	64.0				3.43	5.53	92.2

DATE 1949	PULSE RATE	CO_2 OUTPUT/MIN.	AV. ALVEOLAR CO_2 TENSION	VIRTUAL VENOUS CO_2 TENSION	CO_2 A-V DIFFERENCE	CARDIAC OUTPUT	STROKE VOLUME
	mm.$^{-1}$	*cc.*	*mm. Hg*	*mm. Hg*	*vol. %*	*l.*	*ml.*
H. K.	(*Ht. 68 in., Wt. 163 lb., S.A. 1.88M*^{2}, *Functional Residual Air 1520 cc.*)						
A 5/24	50	168.3	39.26	48.8	4.19	4.02	80.4
	48			49.02	4.25	3.96	82.5
5/26	50	170.0	39.4	48.62	4.06	4.19	83.8
5/27	48	184.0	39.67	48.10	3.75	4.91	102.3
	50			47.72	3.6	5.11	102.2
5/31	50	160.0	39.0	46.53	3.45	4.64	92.8
	52			46.90	3.6	4.45	85.6
	56			46.85	3.58	4.47	79.6
Mean	50.5				3.81	4.47	88.7
Median	50.0				3.68	4.46	84.7
B 5/24	46	168.3	39.26	48.76	4.16	4.05	88.1
5/26	50	170.0	39.40	48.1	3.88	4.38	87.6
5/27	50	184.0	39.67	47.38	3.48	5.29	105.7
Mean	48.7				3.84	4.57	93.8
Median	50.0				3.88	4.38	88

A. Accepted plateaux *B*. Questionable plateau (for definition see text).

RESULTS

Table 1 shows the results obtained in a series of experiments lasting over a period of several weeks. The observed data need little explanation. Venous carbon dioxide gas tension was derived from the values of an apparent plateau, provided that this was not reached earlier than the 12th or later than the 21st second of rebreathing. A plateau was accepted as established if two successive end expiratory samples did not differ by more than 0.06 per cent in concentration. Such experiments are grouped in the table as *A* experiments.

TABLE 2. EXPERIMENTS ON H. K.

BAROMETER	PULSE	RESP. RATE	CO_2 OUTPUT/MIN.	HP[1] ALV. AIR % CO_2	ABOVE—TIME BELOW—END EXPER. SAMPLE				PLATEAU[2]	VOL. CO_2 ADDED ABOVE ARTERIAL LEVELS	A-V DIFF. (CO_2)	CARDIAC OUTPUT
mm. Hg	*min.*$^{-1}$	*min.*$^{-1}$	*cc.*		*sec.*					*cc.*	*vol. %*	*l/min.*
Poorest Results (all experiments on 5/26/49)												
759.3	50	12	170	5.47	6	12	18	24	o	22.8		
					6.31	6.35	6.45	6.55				
	50	11–12			5	11[3]	17	24	o	25.5		
					6.61	2.23	6.44	6.57				
	50				5	10	16	21	+	34.32	4.06	4.19
					6.71	6.67	6.81	6.85				
	50	10–11		5.59	6	11	16	20	?	28.0	3.88	4.38
					6.78	6.62	6.71	6.81				
Best Results (all experiments on 5/3/49)												
763.7	50	12	160	5.32	6	11	16	21	+	34.5	3.45	4.64
					6.64	6.54	6.49	6.49				
	52	12			6	12	16	22	+	32.0	3.6	4.45
					6.88	6.51	6.57	6.59				
	56	11–12		5.56	5	9	14	19	+	36.7	3.58	4.47
					6.62	6.49	6.51	6.55				

[1] Haldane Priestley end expiratory alveolar air sample. [2] + Accepted. o Rejected. ? Questionable. [3] Technical error of uncertain origin.

Details of two experimental runs are given in table 2 which indicates the analyses both when a definite plateau seemed to be attained, and also when in the same subject no evidence was obtained sufficient to indicate such a level clearly. In 'questionable plateau,' differences of 0.1 per cent were allowed in concentrations, or the time limit of 21 seconds for sampling might be exceeded. This time judged at most was 26 seconds. Such experiments are grouped in table 1 as *B* experiments.

The estimated values of the same table need more explanation. Bloods were not examined in these subjects other than for gross evidence of normality. Such procedures were postponed, since it is planned ultimately to attempt determinations of this type simultaneously with the measurement of cardiac

output by the direct Fick procedure. The difference in carbon dioxide content between venous and arterial blood was therefore estimated on the assumption that in these subjects the average slopes of the dissociation curve did not differ greatly from that published for Haldane (3). While this is not likely to be true for each subject, the mean slope for all three subjects is likely to be of the same order as this classical curve. From this additional data, the cardiac outputs and stroke volumes were calculated.

From the average estimations of the A.V. differences for carbon dioxide, those for oxygen may be estimated on the assumption that the R.Q. averaged 0.81. The resulting values for the A.V. difference in oxygen are given in table 3 for comparison with data in the literature. The agreement is striking as is also the consistency of the estimates in table 1. On *subject C.J.M.*, in whom the spread of the results was greatest, the variations were mainly dependent on the subject, for variations in the pulse rate were even greater.

TABLE 3

SUBJECT OR REFERENCE	AVER. PULSE	AVER. A-V CO_2 DIFFERENCE	AVER. A-V CO_2 DIFFERENCE, ESTIMATED OR OBSERVED	
	rate/min.	*vol. %*		
C. W.	56.8	4.11	5.06	
C. J. M.	64.0	3.21	3.96	mean 4.57
H. K.	50.5	3.81	4.70	
McMichael & Sharpey-Shaefer (6)	80.0		4.5	
Stead *et al.* (5)	82.0		4.0	mean 4.33
Cournand (4)			4.5	

Mean stroke for 3 subjects = 87.1; median stroke for 3 subjects = 88.7; mean pulse rate for 3 subjects = 57.1; mean cardiac output = 5.00.

DISCUSSION

The reliability of the values obtained can best be estimated by comparison with those reached by the direct Fick procedure. However, this comparison gives no absolute answer. Table 3 indicates that the average arterio-venous differences for oxygen estimated for these subjects agrees closely with those reported by others for the direct Fick procedure. In *subject C.J.M.* the individual data also agrees well; mean pulse rates, stroke volumes, cardiac outputs, and indices fall within their accepted ranges. The same is not true of the other two subjects. Here the A.V. differences are somewhat greater, cardiac outputs somewhat lower. The most obvious contrast is in the pulse rates which fall in a range very rare in the reported values obtained by the Fick procedure. Consequently, any agreement with the direct values in output would only occur with greatly exaggerated stroke volumes. The contrasts in the two sets of data presumably are due to the greater relaxation obtainable

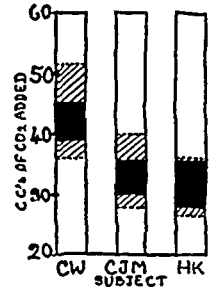
in the absence of catheterization procedures. This is substantiated by the stable consistency of the slow pulse rates in these two subjects. It could be argued that the data agree surprisingly well with those by the Fick procedure. None the less, they seem to imply that cardiac outputs may be lower than is commonly accepted, provided that the subject is fully relaxed.

There is no reason to assume any source of gross error. The concentration of oxygen in the bag at the end of rebreathing (over 30 sec.) was estimated several times and never fell below 16 per cent. At the time of estimation of venous equilibrium it must have been much higher. Evidence of lung-bag mixing was tested in the two subjects with the larger functional residual airs. According to the criterion of Adams and Sandiford (12) it appeared adequate after 12 seconds.

The respiratory pattern was little affected by any of the procedures, except after some 10 or 15 seconds of rebreathing. Usually the subject could notice the turning of the tap, but could not distinguish in the early stages

Fig. 1. BLACK AREA: range in which 'plateau' was obtained. SHADED AREA: range in which 'questionable plateaux' were obtained.

SUBJECT	AVER. A-V DIFFERENCE	FUNCTIONAL RESIDUAL AIR VOLUME cc.
C. W.	4.08	2450
C. J. M.	3.2	1970
H. K.	3.89	1520



between an actual run or dummy procedure. Only after 10 or more seconds did the subject notice any tendency to increase his respiration. Often the change might develop only after 15 or 20 seconds. Consequently, any respiratory response to carbon dioxide accumulation is unlikely to have modified significantly an equilibrium already almost complete.

Nor is recirculation of blood likely to have had serious effects. Baumann and Grollman (13) using right heart puncture found recirculation to commence in 13 to 20 seconds, while Chapman *et al.* (14) more recently by heart catheterization consider that within 19 seconds an error of only 5 per cent would occur in estimation of the tension of a foreign gas.

The evidence of the value of an initial priming of the respiration with an increased concentration of carbon dioxide has been indicated in the presentation of the methods used. The amount of carbon dioxide to be added to the system to produce a rapid approach to equilibrium is rather critical. The values for the three subjects are indicated in figure 1, where the heavy shading indicates volumes giving a real plateau, and the lighter shading volumes adequate

to produce a 'questionable plateau' usable for estimation of cardiac output. They imply that the divergence from the ideal volume should not be much greater than ±5 ml. The actual volume needed is greatest in *subject C.W.* in whom the functional residual volume was greatest and the level of tension needed for equilibrium highest. The amounts needed in the other two subjects are similar since the subject with the higher functional residual air attained equilibrium at the lower carbon dioxide tension.

There is no information available as to the probable success of such procedures in attaining equilibrium in subjects with abnormalities of the lungs. However, further modifications of the method with sampling of alveolar air rather than air from the level of the teeth have recently been made in this laboratory by some of the present group. These will be reported later.[2] Such modifications make the attainment of adequate mixing much easier in normal subjects. While it would be advantageous to utilize experimental periods of shorter duration, it has not been found possible consistently to demonstrate plateaus in shorter periods than 20 seconds with the present procedure. One may therefore suppose that one or other of the two procedures, or a combination of both should be able to solve the problem even in abnormal subjects.

SUMMARY

Breath holding and similar respiratory movements are likely to alter the circulation so their use should be avoided in measuring the rate of blood flow. CO_2 output is insufficient in a rebreathing experiment to raise functional residual lung volumes from arterial to venous levels before recirculation begins. A method is described for obtaining an alveolar venous CO_2 concentration within 21 seconds under suitable conditions, with little disturbance of respiration. The amount of CO_2 which must be added to a lung-bag system to raise functional residual volumes from arterial to venous levels under conditions of normal respiration is rather critical. Use of this method in 3 subjects has shown A-V differences that compare favorably with direct estimations.

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[2] Owing to delays in this manuscript, part of this later work has already been reported in this journal. In general the later work confirms the earlier. It is possible that samples taken after 12 seconds in the present work were modified by recirculation, but data such as that in table 2 indicate that if this be the case, the error often was small.

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Oxygen Metabolism of Moderate Exercise, with Some Observations on the Effects of Tobacco Smoking

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FEW QUANTITATIVE STUDIES of moderate exercise have been detailed enough to define the normal range of individual differences in the several components of oxygen economy under standardized conditions. A recent study by Berg (1) does present the mean and variance of oxygen debt and rate of metabolic recovery for 28 men, heterogeneous as to age and physical status, who did 3 minutes of stool stepping at a rate of about 340 kg. m. per minute. However, the total oxygen cost and net current income were not reported.

The acute effects of tobacco smoking on performance have received sporadic study over a period of some years. Typical experiments are those of Hull, who found (2, p. 142) that in the habitué, smoking increased hand tremor but tended to improve psychomotor performance and increase resistance to fatigue, and Fay (3) who concluded that smoking had no significant effect on reaction time. Juurop and Muido (4) in a study of 4 subjects working on a bicycle ergometer, observed that one or two pre-exercise ciagarettes increased the heart rate during exercise but had no effect on oxygen income during the work period. They did not measure oxygen debt. Kay and Karpovich (5) found that smoking a cigarette did not influence recovery from the local fatigue of a hand dynamometer exercise, if the experiment was adequately controlled. (An earlier experiment by others had reported slower recovery.) Vasoconstriction from smoking was observed by Wright and Moffat (6), Lampson (7) and Hines and Roth (8). A heart rate increase has also been well established (2). McFarland *et al.* (9) found that inhaling a single cigarette increased blood carboxyhemoglobin 2 per cent and 3 cigarettes 4 per cent, resulting in a measurable loss of visual sensitivity.

METHOD AND PROCEDURE

Eighteen young men, all habitual smokers, mostly ages 25 and 26 years and with an average weight of 166 pounds, did 3,070 kg. m. of work in 5 minutes on an electric bicycle ergometer. The rate of movement was 69-pedal rpm. Two such exercise bouts were performed, one immediately after the other, on each of 2 days (at the same time of day) according to the following schema: *I A* = control; *I B* = smoking; *II C* = control; and *II D* = control. Each exercise bout was preceded by 17 minutes of rest and followed by 8 minutes of recovery. Oxygen consumption was recorded during the 7-minute

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rest period, throughout the exercise period and the entire recovery period. During the pre-exercise rest of *test B*, the subject smoked one or 2 cigarettes (mostly 2). All subjects inhaled. They had been requested to refrain from smoking on the experimental day. There is of course no way of knowing the degree of compliance with this request. In the writers' opinion, no subject had smoked as recently as 2 or 3 hours before the experiment.

To balance out any training effect, some subjects did the *Series II* tests before *Series I*. This experimental design made it possible to make 3 types of crucial comparisons: *1*) Experimental vs. control exercise bouts done on the same day $(B - A)$. *2*) Experimental vs. control bouts on one day, corrected for fatigue, training, or practice effects observed in a parallel control vs. control series on another day using identical timing and done at a comparable hour. Algebraically, this amounts to $B - (A + (D - C))$. *3*) Experimental vs. control exercise bouts done on 2 different days, each preceded by a standard exercise and recovery period which presumably reduced possible erratic influences of pre-test factors $(B - D)$.

Oxygen consumption was determined with a closed circuit Metabolar, modified to use $\frac{7}{8}$ i.d. air passages and appropriately sized flutter valves installed next to the face mask. The mask was prepared with fresh rubber cement on the contact surfaces to avoid air leakage. The soda-lime CO_2 absorbent was changed regularly and frequently. All records were measured independently by 2 individuals. The standard error of measurement was .14 to .17 liters for individual current income and debt, so the group averages are subject to a measurement error of the order of .04 liters. Several types of oxygen consumption measures were computed in accord with the following definitions:

Current income. Oxygen in excess of the resting rate taken in during the period of exercise.

Oxygen debt. Oxygen in excess of the resting rate taken in during recovery.

Net oxygen cost of exercise. Current income plus debt.

Debt ratio. Ratio of debt to net oxygen cost, forming a negative index of oxygen transport efficiency.

Maximum intake. Rate of current income at the end of exercise.

Recovery half-time. Time in seconds required for instantaneous net oxygen rate during recovery to drop to half its maximum value, determined from a semi-log plot of net intake vs. time.

RESULTS

A statistical description of the data is given in table 1. The ratios of the mean differences to the standard error of the differences (t ratio) appear in table 2. Since a t of 2.12 is required for statistical significance at the 5 per cent level of confidence, it is clear that none of the comparisons shows a difference

larger than can be accounted for by random sampling error. It should be mentioned that these tables are based on the results of 17 cases, since there was evidence of oxygen mask leakage in the *A* and *C* tests of one subject. The net oxygen income of this subject was greater and the debt less in the smoking test; hence the loss of this record does not bias the conclusions.

TABLE 1. STATISTICAL DESCRIPTION OF OXYGEN COST OF EXERCISE (IN STPD LITERS) AND DEBT INDICES

STATISTIC	TEST							
	I-A		I-B		II-C		II-D	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Current O_2 income	4.67	.74	4.80	.67	4.56	.59	4.85	.47
O_2 debt	1.25	.14	1.32	.26	1.24	.24	1.29	.29
O_2 cost of exercise	5.93	.67	6.12	.62	5.80	.67	6.15	.58
Debt ratio (per cent)	21.40	3.23	22.17	4.02	21.33	3.32	20.97	4.21
Max. intake rate (per min.)	1.03	.11	1.15	.22	1.05	.13	1.17	.11
Recovery rate (½ T-sec)	45.3	7.2	47.5	11.5	47.4	7.5	45.2	12.5

TABLE 2. MEAN DIFFERENCE IN OXYGEN ECONOMY OF EXERCISE RESULTING FROM CIGARETTE SMOKING, AND RATIO *t* OF THE DIFFERENCE TO ITS STANDARD ERROR

STATISTIC	TESTS COMPARED					
	First method B-A		Second method B-[A + (D-C)]		Third method B-D	
	Difference	*t*	Difference	*t*	Difference	*t*
Current O_2 income	.13	.86	−.16	1.19	−.05	.37
O_2 debt	.07	1.04	.02	.26	.03	.37
O_2 cost of exercise	.19	1.17	−.15	.91	−.02	1.44
Debt ratio (per cent)	.77	.97	1.13	1.46	1.20	1.47
Max. intake rate (per min.)	.12	1.05	0	1.28	−.02	.32
Recovery rate (½ T-sec)	2.2	.71	4.4	1.42	2.3	1.03

A *t* ratio of 2.12 is required for statistical significance at the 5 percent level of confidence; a ratio of 2.92 is required for significance at the one per cent level.

The tables given here are based on the measurements of the more experienced of the two technicians.[1] Similar statistics have been computed with the other set of measurements with the same results; comparison showed no statistically significant effect of the experimental factor.

DISCUSSION

While the exercise used was not maximal, most of the subjects complained of fatigue at the end of exercises *B* and *D*. It was sufficient to produce an

[1] The writers are indebted to Janice DeMoor for making these measurements.

oxygen debt of at least one liter in all cases and 1.5 liters in a third of the cases. The oxygen debt from a lighter work load, namely the stool-stepping exercise of Berg (1), has been shown to be reduced significantly by athletic training (10, p. 240). The factors responsible for the smaller oxygen debt in trained men presumably include improved local oxygen supply and utilization in the working muscles even in the absence of maximal demand on the oxygen transport system. There may also be a faster initial adjustment to the work requirement, made possible by the more adequate oxygen transport system resulting from conditioning. The known acute effects of smoking, namely peripheral vasoconstriction (suggesting poor utilization) together with the added small effect of 2 or 3 per cent loss in oxygen capacity due to carboxyhemoglobin, plus the general circulatory inefficiency implied by the tachycardia of smoking, would all operate in the opposite direction to athletic training and thus give some expectation of a larger oxygen debt in moderate exercise as a result of smoking.

It is of course quite possible that positive results might have been secured with a much more severe exercise, although this is unlikely since Juurop and Muido had negative findings with respect to oxygen income for work loads as high as 1800 kg. m. per minute. A considerably longer smoking period might have led to positive results. Insofar as the monoxide factor is concerned, there seems to be no reason to believe that the acute effects would be any different in habitual smokers and non-smokers. Chronic effects would presumably be small because of acclimatization (11, pp. 152–154). The acute cardio-vascular changes occur in habitual smokers, although there is an acquired tolerance to nicotine.

In the present investigation, the effects of intra-individual and inter-individual differences in response were minimized by having each subject do all 4 parts of the experiment. The standard error of the difference averaged .14 liters in the case of current oxygen income and about half of this in the case of oxygen debt. As pointed out earlier, only .04 liters of this is due to error of measurement; hence, the chief sources of error are fluctuation in the response of individuals from one test to another and sampling error due to the fact that data from only 17 subjects were available. Even though these errors would be reduced by testing a larger number of subjects, detailed study of the results gives little basis for the opinion that this would lead to statistically significant differences. By using the second and third methods of control, the data do show a fairly consistent physiological picture of slightly less efficient oxygen transport due to smoking, namely .05 to .16 liters less current oxygen income, .02 to .03 liters more oxygen debt, 1.1 to 1.2 per cent larger debt ratio and 2 to 4 seconds slower rate of debt pay-off. These differences, however, are quite small and definitely not significant.

It is of interest to note that the average efficiency of the exercise, cal-

culated as the ratio of work done to the net total oxygen cost of the work, assuming an *RQ* of unity, is 23.8 per cent (S.D. = 2.54). This is a fairly typical result for efficiency of bicycle riding. As might be expected, the average oxygen debt (17.0 cc./kg., S.D. = 3.1) is significantly larger than Berg's figure of 11.7 cc. per kilogram obtained with an exercise much lighter than that used in the present study. The time constant of recovery, 46.4 seconds half-time, is significantly slower than Berg's half-time of 31.3 seconds. He observed that the half-time tended to be slower with severe work, although it was independent of rate of work in light exercise.

SUMMARY

With the use of a closed-circuit metabolism apparatus, the average net efficiency of a 5-minute cycling exercise at 614 kg.m. per minute was found to be 23.8 per cent. The oxygen debt, 17 cc. per kilogram body weight, was paid off with a half-time recovery rate of 46.4 seconds. The mean ratio of debt to net oxygen cost of the work was 0.215. Each of the men did the test exercise 2 times on each of 2 days. On one of the days the second exercise was preceded by the smoking of one or 2 cigarettes, a procedure which had no statistically significant effect on exercise metabolism in any of the measured aspects.

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Postgastrectomy and Postvagotomy Syndrome[1]

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THE TERMS 'dumping, postgastrectomy, postcibal or postprandial syndrome' are synonyms for a vaguely understood condition which follows subtotal gastrectomy in from 5 to 40 per cent of patients. A similar condition was observed after vagotomy alone or in combination with gastroenterostomy by Dragstedt (1), Kirsner (2) and Paulson and Gladsden (3). Alvarez (4) has observed the syndrome in unoperated persons. Evensen (5), Schechter and Necheles (6) and Adlersberg and Hammerschlag (7) have reviewed the recent literature and have added their observations on normal subjects and on patients.

The syndrome may be divided into two phases; the early phase immediately after ingestion of food, and the late phase from $1\frac{1}{2}$ to 3 hours after meals. The first phase is not related to changes in the blood sugar, but the second phase is always accompanied by hypoglycemia. Clinical symptoms of the first phase may appear as nausea, a feeling of fullness, belching, abdominal cramps and diarrhea. Generalized symptoms, such as weakness, dizziness, an unpleasant sensation of warmth throughout the body, cold sweat, headache and palpitations are common to both, the early and the late phase. It has been observed by Schwartz *et al.* (8) and by Schechter and Necheles (6) that in patients suffering from the syndrome, the first, second, or both phases of the syndrome can be reproduced by oral administration of sucrose or glucose. Fructose given by mouth would produce the first but not the second phase, with no unusual changes in blood glucose levels (6), thus lending doubt to the hyperglycemic theory of Glaessner *et al.* (9, 10).

Reid (11) believes that cerebral centers can be activated through olfactory and gustatory mechanisms, thereby decreasing the blood sugar through stimulation of insulin output. He states that, if during oral glucose-tolerance tests the animal was allowed to sniff or taste meat, blood glucose levels fell more rapidly, and that, if no glucose was given and the animal allowed to sniff meat, a

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significant fall in blood sugar occurred. If these observations could be confirmed, their role in the production of the postprandial syndrome would have to be considered.

We were unable to find in the literature controlled studies in animals on the postprandial syndrome. Therefore, we have attempted to duplicate the condition in the dog and to study the mechanisms involved under more controlled conditions than is possible in man.

EXPERIMENTAL

Normal adult male and female mongrel dogs were given oral and intravenous glucose- and fructose-tolerance tests, after which the following aseptic operative procedures were performed on 10 dogs: *1*) Subtotal gastric resection of the Polya type, 3 dogs. On one of these dogs a supradiaphragmatic bilateral vagotomy was performed 2 months later. *2*) Subtotal gastric resection of the Hofmeister type and an entero-enterostomy, $2\frac{1}{2}$ months later, one dog. *3*) Gastrojejunostomy and enteroenterostomy, one dog. *4*) Pyloroplasty of the Heineke Mikulicz type in one dog, and of the Finney type in one dog. *5*) Bilateral supradiaphragmatic vagotomy in 3 dogs, with an additional gastrojejunostomy in 2 of them. After the animals had recovered from the operation, and were in good condition, tolerance tests were resumed from one to 12 days, in most experiments 6 days, postoperatively. The dog with subtotal gastrectomy of the Hofmeister type died with a perforated marginal ulcer one week following the operation (25% incidence, see 12).

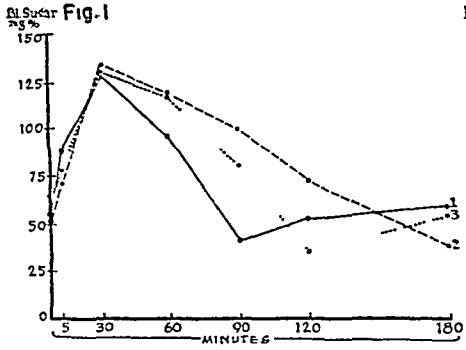
Glucose and fructose determinations were performed in duplicate by the Somogyi and the Corcoran and Page (13) methods, respectively. Blood samples were taken after 24 hours' fasting and after administration of the sugar, as indicated in the charts. The dose of glucose or fructose given was 1.75 gm/kg. for oral, and one gm/kg. for intravenous tests, in 20 to 30 per cent solutions. Fructose was used because in previous work on man we have found that it was able to produce the first phase of the postprandial syndrome (6). Fructose leaves the blood rapidly, as was indicated by the values of blood fructose and blood glucose following its oral or intravenous administration.

Gastric emptying times were determined by fluoroscopy at hourly intervals after feeding a standard barium meal (14). The effects of olfactory and gustatory stimulation on blood sugar were studied in one normal animal and in one dog with subtotal gastrectomy, following the procedure of Reid (11). Because of a possible influence of posture on gastric emptying, 2 dogs with subtotal gastrectomies were trained and held in the erect position during pre- and postoperative glucose-tolerance tests, thus assuming the upright position of man.

In order to check the completeness of vagotomy, insulin tests were done on the vagotomized animals according to the Hollander procedure (15, 16).

RESULTS

Symptoms of the postprandial syndrome were observed in only one of 10 dogs (*dog 1*). In this animal preoperatively, i.v. glucose-tolerance tests yielded normal results, but the oral glucose-tolerance test showed a distinct tendency toward hypoglycemia (fig. 1). Thus, 90 minutes after oral administration of the glucose the blood sugar dropped to 40 mg. per cent. Likewise, following a Polya-type subtotal gastrectomy, blood sugars dropped to even lower levels (36 mg. %), and vomiting occurred 2 to 3 hours after feeding a mixed meal, at the time when hypoglycemia appeared in the oral glucose-tolerance test. Thus it seems, that in this animal, the second phase of the



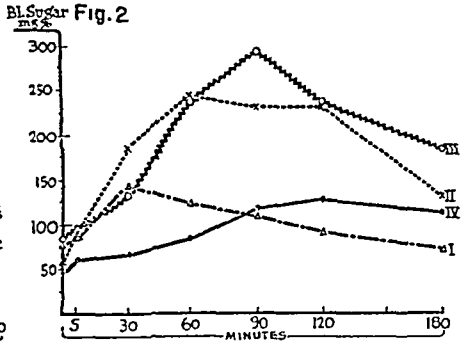


Fig. 1. HYPOGLYCEMIC TENDENCY in *dog 1* before and after Polya type subtotal gastrectomy Oral glucose-tolerance tests: *Curve 1*, Control, 1–20–49; Polya operation 1–21–49. *Curve 2*, 2–4–49 *Curve 3*, 2–10–49.

Fig. 2. GLUCOSE TOLERANCE TESTS in *dog 2* before and after Polya-type subtotal gastrectomy and supradiaphragmatic vagotomy. Oral glucose tolerance tests: *Curve* I, Control, 9–28–48; Polya operation, 10–22–48. *Curve* II, 12–16–48; vagotomy, 12–20–48. *Curve* III, 12–28–48. *Curve* IV, 1–4–49

postprandial syndrome was present. Emptying time of a barium-food meal was 4 hours in this animal after the Polya operation. This is shorter than the 5 to 6 hours' emptying time in normal non-operated dogs, yet not fast enough to be called dumping. The initial emptying of the meal did not appear to be unusually fast.

In none of the other 9 dogs did we observe symptoms referable to the postprandial syndrome, either of its first or of its second phase. Hypoglycemic values of blood sugars in the intravenous or oral glucose-tolerance tests were not observed in any of these animals, either before or after the various operations. However, the oral glucose-tolerance curves were higher and more sustained in 3 out of 4 dogs following subtotal gastrectomy and even higher when transthoracic vagotomy had been added, as illustrated in figure 2. Similar results as shown in figure 2 were obtained in 2 out of 4 vagotomized dogs, lasting for 2 weeks following vagotomy. Of 2 other dogs with vagotomy plus

gastrojejunostomy, this condition was found to be present in one animal. In all vagotomized animals the insulin test was negative.

The results of pre- and postoperative oral glucose-tolerance tests on 2 dogs held in the erect position, one Polya and one Hofmeister type of subtotal gastric resection, were similar to the results of tests done in the normal horizontal position of the same animal, and to those shown in figure 2.

The intravenous fructose-tolerance tests showed normal fructose curves before and after the various operations. However, the 5-minute *glucose* values showed a sharp rise in each of the intravenous fructose-tolerance tests. In order to see whether this initial rise of blood glucose was specific for the fructose, or whether it might be the effect of a hypertonic solution, the same volume of an equimolecular solution of sodium sulfate was administered i.v. Sodium sulfate gave a more sustained initial rise in the blood glucose, complicated however by a short period of shock, lasting 2 to 3 minutes. The effect

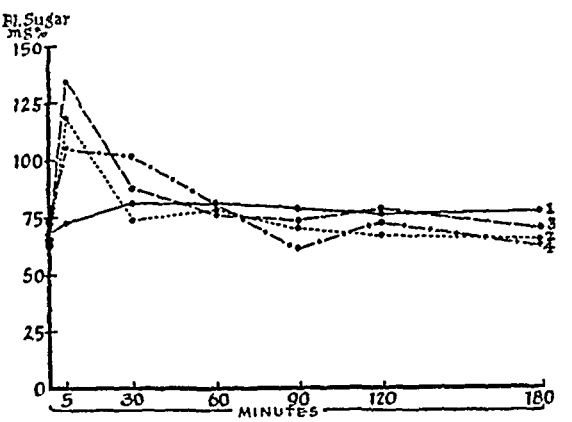


Fig. 3. BLOOD GLUCOSE VALUES in intravenous fructose-tolerance tests and following intravenous sodium sulfate. *Curve 1*, saline control, *dog 3*. *Curve 2*, preoperative, *dog 4*, 8–10–48; Hofmeister-type subtotal gastrectomy, *dog 4*, 8–13–48. *Curve 3*, postoperative, *dog 4*, 10–12–48. *Curve 4*, preoperative, sodium sulfate, *dog 5*.

of i.v. injection of fluid was checked, and it was found that the same volume of normal saline solution administered intravenously, did not affect blood sugar levels (fig. 3). The initial rise of blood sugar following intravenous injection of fructose was not prevented by vagotomy, nor by blocking the autonomic ganglia with tetraethylammonium chloride (Etamon). Thus, two possible explanations for this phenomenon remain, release of epinephrine causing glycogenolysis, or direct release of glucose from the liver.

In observations on 2 dogs, one normal and one with a Polya type subtotal gastrectomy, we could not duplicate the effects on fasting blood sugar levels or on the oral glucose-tolerance curve of sniffing and tasting, as observed by Reid (11).

Gastric emptying times in 2 Polya dogs averaged 5 hours (4 to 6 hours). Strauss *et al.* (17) and Barnes (18) have reported emptying times as short as 15 minutes in patients with the dumping syndrome. Evensen (5) was unable to correlate gastric emptying times and abnormal blood sugar levels. It is of interest to point out here that rapid emptying of the stomach can be pro-

duced by section of the left phrenic nerve in man (19) and in the dog (20), without evidence of the postprandial syndrome. In such dogs, the initial emptying of the barium meal was particularly rapid, truly deserving the name of dumping, yet no symptoms were noticed (20).

Several dogs were reoperated and the stoma sizes were found to have attained a relatively uniform size, that is, the large stoma was smaller and the small stoma larger.

DISCUSSION

Custer *et al.* (21) believe that the small stoma of the Hofmeister operation reduces the incidence of the postprandial dumping syndrome, but Ingelfinger (22) has not been able to find a relationship between type of operation and incidence of the dumping syndrome. In our experiments, the early phase of the syndrome in which dumping can occur was not observed following any of the various operative procedures employed. Even in dogs (one after a Polya and one after a Hofmeister operation) held in the upright position during the oral glucose-tolerance test, neither dumping nor hypoglycemia was apparent. The late postprandial syndrome was observed in only one out of 10 dogs. (See fig. 1.) This animal had a Polya-type subtotal gastrectomy. No dumping of the barium meal was seen postoperatively. The significant difference between this dog and the other 9 dogs seemed to be in temperament. Pavlov (23) has stressed the importance of the different temperaments of dogs on physiological responses. Generally, we selected gentle dogs, which were easily managed and trained. *Dog 1* was selected because of its nervousness, high spirits and activity. It was noted that his oral glucose-tolerance curve before operation, unlike that of the other dogs, showed a hypoglycemic tendency. Thus, this animal may have been predisposed to the development of the syndrome. It has been noted (6) that patients who developed the postprandial syndrome after subtotal gastrectomy are highstrung and tense, but preoperative data on oral glucose-tolerance tests in such patients are lacking.

The intravenous glucose-tolerance tests performed before and after the various operations on the stomach, including vagotomy, yielded almost identical normal curves, indicating that carbohydrate metabolism had not been changed by the various operations. Different results were obtained with the oral glucose-tolerance test. In one dog, it showed a distinct hypoglycemic response before and after subtotal gastrectomy. In the other 9 dogs, normal oral glucose-tolerance tests were obtained before operation. However, a greater and more prolonged response to the oral glucose-tolerance test was obtained in 7 animals following operations as varied as subtotal gastrectomy, vagotomy and pyloroplasty. When vagotomy was added to subtotal gastrectomy, the oral glucose-tolerance curves showed a further increase in one dog. The onset

and the duration of the greater and prolonged response to the oral glucose-tolerance test varied in different animals. The onset of a decreased tolerance to oral administration of glucose was observed between 6 and 31 days after the various operations, and tolerance was found to have returned to normal within 20 to 35 days after the various operations.

Quigley *et al.* (26) have found that vagotomy produced no change in glucose tolerance. However, their tests differed from ours, as they were performed one to 6 months after vagotomy, and all of them were made by the intravenous route. Thus we must consider acute factors of the operation, which may have produced a prolonged and elevated glycemic response in our experiments.

Since stimulation of the right vagus will reduce blood sugar levels (24), it may be that section of the vagus nerves will allow for a transient elevation of blood sugar levels until other regulations of blood sugar and insulin have taken over, which appeared to occur 20 to 35 days after the various operations (fig. 1). It has been shown by Crider and Thomas (25) that a 50 per cent reduction in pancreatic enzymes follows vagotomy, and Hollander (16) states that the insulin test for vagal integrity is unreliable for the first 2 weeks following operation.

The wide stoma produced in most subtotal resections permits rapid emptying of the glucose solution into the small intestine, and thus more rapid absorption and higher blood sugar levels can be expected. However, following vagotomy, gastric-emptying time is usually prolonged. It is not possible to explain both, increased blood sugar level and sustained increase of the blood sugar, by more rapid intestinal absorption. The normal intravenous glucose-tolerance tests show that the various operations did not decrease the ability to the animals to store or metabolize glucose. Therefore the diabetic-like blood sugar curves obtained within the first 3 to 5 weeks after the operations must be ascribed to an effect of the surgery on absorption of glucose in the gut, and to effects of the postoperative condition of the dog on the liver. It is generally believed that the normal dog can absorb within 3 hours 1.75 gm/kg. of glucose administered orally. More rapid absorption could produce a higher blood sugar curve or a more sustained curve, but hardly both. Subtotal resection, gastroenterostomy and vagotomy are operations which are usually followed by gastritis and jejunitis, and the surgical procedure by itself may affect physiological regulations. It is quite possible, therefore, that the shutoff regulation of the glucose supply to the blood from the liver, which is produced by high blood sugar levels, did not function well for the first few weeks after the operation. It is possible that the hypertonic glucose solution given orally, sets up sympathetic reflexes from an inflamed stomach and jejunum, which led to an increased mobilization of liver glycogen.

As the body adjusts regulations and as the acute irritation lessens, normal oral glucose-tolerance curves may reappear.

We have been unable to reproduce the results obtained by Reid (11) on dogs in sniffing and tasting experiments. If the higher centers were as reactive as Reid contends to sniffing and tasting alone in lowering blood sugar, then one might expect dogs and possibly humans to develop the second phase of the dumping syndrome before the meal begins.

SUMMARY

We have attempted to reproduce the postprandial syndrome in the dog. Ten dogs were subjected to various types of gastric resection, gastroenterostomy, pyloroplasty and vagotomy. Only one of 10 dogs studied pre- and postoperatively developed symptoms and signs of hypoglycemia and vomiting referable to the second phase of the postprandial syndrome. In 7 dogs, following operations as varied as subtotal gastrectomy, vagotomy, gastroenterostomy, and pyloroplasty, oral glucose-tolerance tests showed higher and more prolonged curves than preoperatively. When transthoracic vagotomy was added to subtotal gastrectomy, the oral glucose-tolerance curves showed a further increase in one dog. We were unable to confirm the reported effect of olfactory or gustatory stimulation on blood sugar. Intravenous injection of hypertonic fructose or sodium sulfate solution caused a distinct transient rise in the blood glucose. We have not observed in the dog in these experiments the dumping stomach, i.e. the early phase of the postprandial syndrome.

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Significance of Changes in Extracellular Fluid Volume During Insulin Therapy for Mental Disease

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RAPID GAIN IN WEIGHT is well known to occur in patients given insulin therapy for mental disease. In order to gain some insight into the mechanisms involved in this change, it was, therefore, considered of interest to study the relation between changes in weight and in extracellular fluid volume in patients so treated.

MATERIAL AND METHODS

Nine patients, ranging in age from 22 to 55 years, were studied; 7 were men. The diagnoses varied (table 1, fig. 1). Measurements of extracellular fluid volume were made with the patients in the basal state using the thiocyanate method (1) acording to a procedure described previously (2). The treatment used was subcoma insulin therapy, given one to 3 times daily.

OBSERVATIONS

The extracellular fluid volumes before treatment were between 11.7 and 19.5 l., or 20.2 and 28.4 per cent of the body weight (table 1). During treatment the values rose to between 19.1 and 21.5 l. or 22.3 and 29.6 per cent of the body weight. Changes in extracellular fluid volume were in the same direction as changes in weight but not strictly in proportion except in the initial period of treatment (fig. 2). In one patient, (*Case 2*, table 1, fig. 1) in whom clinical relapse and loss of weight began immediately after the end of the period of treatment, body weight and extracellular fluid volume both decreased, but rose again when treatment was resumed.

DISCUSSION

Previous work (2) indicated that the gain in weight observed during the course of electroshock therapy was largely due to retention of water; it was concluded that stimulation of the adrenal cortex during the treatments re-

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sulted in the elaboration of increased amounts of steroid hormones resembling desoxycorticosterone in action. In the present study on insulin therapy it has been shown that the gain in weight likewise is associated with retention of water. Other work has shown that insulin therapy gives rise to changes indicative of adrenal cortical stimulation, such as lysis of blood eosinophilic cells (3) and lymphocytes (4) (5). More pertinent in this connection is the fact that patients given insulin therapy may exhibit a decrease in sodium concentration of the sweat (6), indicating an increase in the production of electrolyte-regulating steroid hormones. A valid conclusion, therefore, is that the water retention of insulin therapy is consistent with one effect of increased adrenal cortical activity. The considerably greater amount of water retained during insulin therapy as opposed to electroshock therapy (2) is possibly to be explained by the fact that patients given the former have 30 to 90 episodes of adrenal cortical stimulation during a month, whereas patients given electroshock have usually no more than a dozen in this interval. It is apparent, however, that insulin and electroshock therapy have much in common in regard to their effects on adrenal cortical function. It is not to be concluded that all of the gain in weight observed in patients receiving insulin is the result of an increase in extracellular water; many data are available which show that insulin causes also the formation of additional protein (7).

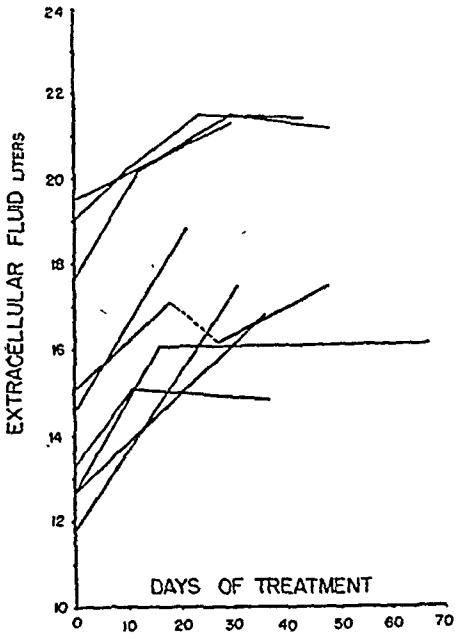

Fig. 1. GAIN IN EXTRACELLULAR FLUID VOLUME during insulin therapy. Broken line indicates interruption of treatment in one case, with rapid relapse and loss of weight.

That retained extracellular water distributes itself in the body roughly in proportion to the collogen content of tissues is well known. Accordingly, the two tissues, i.e. skin and lung, which have the largest relative collogen contents, are the ones most likely to show the effects of water retention during the course of insulin therapy. Subcutaneous edema is common; the development of dyspnea or frank pulmonary edema is well known also and may require the use of ammonium chloride for its amelioration. As frequently occurs in other conditions in which salt and water retention occur, an increase in heart-size as measured roentgenographically has also been found in schizophrenic patients given insulin therapy (8, 9, 10).

TABLE 1

CASE	AGE	SEX	WEIGHT	EXTRA-CELLULAR FLUID	RATIO	DIAGNOSIS	REMARKS
			kg.	*liters*			
1	23	M	73.0	17.7	24.2	Schizophrenia	Before treatment
			73.9	20.2	27.4		After 12 days of treatment
			80.5	21.5	26.7		After 29 days of treatment
			80.7	21.2	26.3		After 49 days of treatment
2	21	M	65.5	15.1	23.1	Schizophrenia	Before treatment
			68.0	17.1	25.2		After 18 days of treatment
			67.3	16.2	24.1		After 9 days of no treatment
			73.0	17.5	24.0		After 22 days of additional treatment
3	30	M	66.9	19.0	28.4	Schizophrenia	Before treatment
			70.7	20.2	28.6		After 10 days of treatment
			75.6	21.5	28.0		After 24 days of treatment
			76.6	21.4	27.9		After 42 days of treatment
4	55	F	60.7	13.3	21.9	Psychoneurosis; reactive depression	Before treatment
			65.2	15.1	23.2		After 11 days of treatment
			66.4	14.8	22.3		After 37 days of treatment
5	27	M	52.7	12.7	24.1	Schizophrenia	Before treatment
			57.8	16.1	27.8		After 16 days of treatment
			65.0	16.2	25.0		After 68 days of treatment
6	38	M	84.6	19.5	23.0	Alcoholic psychosis	Before treatment
			86.2	21.3	24.8		After 30 days of treatment
7	33	F	57.7	12.7	22.0	Psychoneurosis; obsessive-compulsive	Before treatment
			61.8	16.8	27.2		After 36 days of treatment
8	25	M	57.8	11.7	20.2	Schizophrenia	Before treatment
			62.3	17.5	28.1		After 31 days of treatment
9	28	M	60.5	14.6	24.2	Psychoneurosis; obsessive-compulsive	Before treatment
			63.6	18.8	29.6		After 21 days of treatment

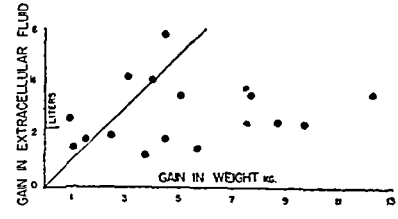

Fig. 2. RELATION BETWEEN INCREASE in extracellular fluid volume and gain in weight during insulin therapy.

SUMMARY AND CONCLUSIONS

Changes in extracellular fluid volume during the course of insulin have been studied by means of the thiocyanate method in 9 patients. Early gain in weight is associated with corresponding increases in extracellular fluid content but subsequent gains in weight are not. The changes found are probably a result of increased production of some adrenal cortical hormones.

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Metabolic Efficiency of Exercise in Relation to Work Load at Constant Speed[1]

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SHORTLY AFTER THE TURN OF THE CENTURY, following the development of the bicycle ergometer and the methodology of indirect calorimetry, there was evidenced an interest in the efficiency of the working human body as a machine. Efficiency has usually been defined as the ratio of external work accomplished to the metabolic cost of that work over and above the resting metabolism. Four problems that have received continuing attention have been: *a*) the actual efficiency as such, *b*) the relation between diet and efficiency, *c*) the influence of speed of movement on efficiency, and *d*) the influence of magnitude of work load on efficiency. Even though the last-named problem has a relatively long history of investigation, it is still unsettled.

Benedict and Carpenter (1) in 1909 varied the work load on a magnetic brake bicycle ergometer, but unfortunately did not standardize the rate of movement very well. In the one subject whose work load ranged from 43 to 800 kg.m/min., efficiency did not change appreciably from the mean value of 21 per cent. Four years later, Benedict and Cathcart varied the work load from 185 to 1000 kg.m/min. with the rate of movement standardized at particular speeds in the range of 60 to 128 pedal rpm. While 5 subjects were used in the study, most of the work was done on one man, a professional cyclist. In many of the experiments his efficiency increased at the higher work loads; for example, at 72 rpm it went up from 26.0 per cent to 28.7 per cent. Some of the experiments showed a decrease, as for example, from 25.1 per cent to 23.2 per cent at 104 rpm, and from 26.0 per cent to 22.4 per cent at 108 rpm (2). These investigators were of the opinion that on the whole, efficiency tended to increase

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with greater work loads because the energy required to maintain the position of the body on the bicycle became a smaller fraction of the energy cost of the work at the higher loads.

In a subsequent article published in 1922 (3) Cathcart contended that efficiency reaches an optimum at about 150 kg.m/min. and then falls off at heavier work loads because of the larger static component. Campbell, Douglas, and Hobson (4) in 1920 tested two subjects at 50 pedal rpm and observed that they were less efficient at 1056 kg.m/min. than at 704 kg.m/min. The change, however, was small—from 24.8 per cent to 24.1 per cent in mean percentage. In 1923, Duffield and McDonald (5) reported that changing the work load from 170 to 900 kg.m/min. did not appreciably alter the efficiency of their one subject at 40 rpm, 63 rpm, or 85 rpm. No evidence for an optimum load was found.

Experiments reported by Hansen (6) in 1927 on a single subject showed higher efficiency with greater work loads. A typical change was that observed at 59 pedal rpm—from 16.8 per cent at 220 kg.m/min. to 19.1 per cent at 438 kg.m/min. to 21.0 per cent at 1100 kg.m/min. Similar results were secured at other speeds ranging from 38 to 102 rpm. Dickinson (7) two years later concluded that efficiency was not appreciably affected by work load. Her experiment was limited to observations on a single subject who worked at the rate of 33 pedal rpm. The efficiency was 22.0 per cent at 61 kg.m/min. and somewhat lower, i.e. 20.6 per cent, at 384 kg.m/min. At intermediate work loads there were no consistent changes. Recently Winslow and Herrington (8) have presented data on two subjects working at 38 rpm. Efficiency decreased with increasing load, ranging from 34 per cent at 140 kg.m/min. to 24 per cent at 490 kg.m/min.

Most of these investigators have studied one or at most very few individuals, and have depended on a presumed 'steady state' condition in contrast to determination of the total oxygen cost of the work.

METHOD AND PROCEDURE

Nine experienced cyclists exercised on a bicycle ergometer at approximately 690 kg.m/min. On a subsequent day, at a corresponding hour, they exercised at approximately 920 kg.m/min. In both cases the rate of movement was 61 pedal rpm. The ergometer was of the eddy current type, calibrated by substituting a pulley for the pedals and driving the instrument by means of falling weights. A redesigned seat equipped with a back rest aided in securing relaxation and comfort during rest.

Oxygen consumption was determined with a closed circuit clinical-type metabolism apparatus that had been modified to reduce air friction. Air passages were increased to 7/8 inch cross section, including oversize flutter valves installed close to the face mask. Recording of oxygen consumption was con-

tinuous during 8 to 10 minutes pre-exercise rest, the 6 minutes of exercise, and 35 minutes of recovery. Recovery records were measured in detail—at 15-second intervals during the first minute, 30-second intervals to the 3rd minute, one-minute intervals to the 8th minute, and 2-minute intervals thereafter—to permit the study of recovery curves.

EXPERIMENTAL RESULTS

It was found that the recovery data could be fitted with an equation of the form

$$y = a_1 e^{-k_1 t} + a_2 e^{-k_2 t}$$

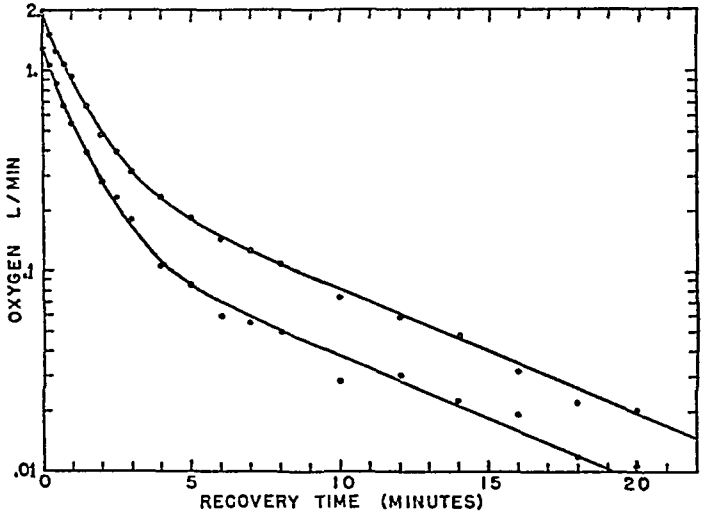

Fig. 1. TWO-COMPONENT exponential recovery curves. *Upper curve:* work at 920 kg.m/min. *Lower curve:* work at 690 kg.m/min.

where y is the rate of oxygen consumption at time t (in excess of the resting rate established near the end of the recovery period), and $a_1 + a_2 = a_0$ (the rate of oxygen consumption at the end of exercise). The term $a_1 e^{-k_1 t}$ presumably represents the *alactic* component of the recovery curve, the amount of alactic debt being equal to a_1/k_1. The term $a_2 e^{-k_2 t}$ is the so-called *lactic* component. Thus the total oxygen debt Q is equal to $a_1/k_1 + a_2/k_2$.

As may be seen in figure 1, the average recovery data from both the 690 and 920 kg.m/min. exercises show a satisfactory fit with the formula using the same velocity constants for both sets of data. This is confirmed by the fact that when the recovery curves are fitted to the data of each individual, there is no statistically-significant difference between the velocity constants of the easier and harder exercises.

Various other aspects of the individual recovery curves for the two exer-

cises have been compared statistically; the results are summarized in table 1. Perhaps the most salient difference is the large increase in 'lactate' component of the debt in the case of the more severe exercise. The 'alactic' component has also increased to a statistically significant degree, but the lactic component increase is, on the average, more than twice as large as the alactic. Comparison of the individual ratios of lactic component to total debt yields a t ratio of 3.1 between the two exercises, which is a statistically significant difference.

The efficiency, defined as the ratio of external work accomplished to the net metabolic cost of the work, decreases from .212 for the lighter work to .193 for the heavier work. While this represents a reduction of only 9 per cent,

TABLE 1. STATISTICAL SUMMARY OF METABOLIC RECOVERY CURVES FROM TWO LEVELS OF EXERCISE

WORK RATE STATISTIC	MEAN	σ	MEAN	σ	PER CENT INCREASE	t RATIO
	690 kg.m/min.		*920 kg.m/min.*			
a_1	1.082	.151	1.565	.259	44.6	5.0
k_1	1.059	.123	1.107	.235	.5	.1[1]
'alactic' debt	1.03	.17	1.43	.12	38.8	6.4
a_2	.181	.068	.402	.123	122.0	11.5
k_2	.125	.025	.144	.019	15.3	1.2[1]
'lactic' debt	*1.56*	*.71*	*2.82*	*.76*	*80.8*	*8.1*
a_0	1.263	.123	1.967	.244	55.8	6.1
Total O_2 debt	2.52	.58	4.45	.85	76.8	10.1

Oxygen measures are in STPD liters. The t ratios were computed from the distributions of differences.

[1] Indicated t ratios are not statistically significant. All others are highly significant.

it is a highly significant decrease since the t ratio is 5.4. It should be noted that any practice effect would have acted to reduce this difference.

DISCUSSION

If it can be assumed that the lactic debt mechanism is less efficient than the alactic mechanism, the relatively greater increase in lactic debt at the heavier work load would account for the reduced efficiency. It is doubtful if strained posture and increased general muscular tension can be justified as an explanation. The difference between the total oxygen cost of the heavier work at the observed efficiency of 19.3 per cent and the calculated oxygen cost for the 21.2 per cent efficiency found with the lighter work amounts to 1.2 liters, or .2 liters/min. Sitting on the bicycle with arms tense against the handlebars and legs sufficiently tense against the pedals to cause pressure against the back of the seat was observed to increase oxygen consumption only .01 to .02 liters/

min. It is of course possible that coordination is poorer with the heavier load, although the writers' subjective impression from doing the two exercises is that this was a minor factor.

The present experiment shows that the proportion of slow component or lactic debt to total oxygen debt increases with increased severity of exercise, even though the amount of alactic debt—1.2 to 1.6 liters— is well under the maximum limit for alactic debt. (The actual limit is uncertain since the extent of individual differences has not been investigated. Margaria and Edwards (9) consider the limit to be 3 or 4 liters.) With fully half the total debt being of this slow component type at 690 kg.m/min. and two-thirds at 920 kg.m/min., it seems likely that the lactic debt plays a rather important role in recovery from even relatively moderate exercise. Possibly there are individual differences, quantitatively, since the proportion ranges from 37 to 76 per cent with the ligher exercise and 60 to 79 per cent with the more severe exercise.

There are data in the literature that are in agreement with this finding when analyzed by the method employed in the present study. Two of the Margaria, Edwards and Dill (10) protocols, *numbers 1* and *2*, involve a rate of work of the order of 800 to 1000 kg.m/min., and these data show 70 to 75 per cent lactic debt component. Some of the data from table 1 from Hill, Long, and Lupton (11) represent work loads of the order 1200 to 1400 kg.m/min., and show 40 to 45 per cent lactic component in the total debt. With more severe work, the proportion rises to 60 to 70 per cent. It should be noted that in each of these studies the results are from only a single subject, and the work was running rather than cycling. Berg (12), using a stool-stepping exercise, reported no lactic component in his recovery curves. His exercise, however, was very light—about 340 kg.m/min.—and recovery was followed for only 6 or 8 minutes. The data from his figure 1, when reanalyzed using the minimum oxygen consumption rate near the end of recovery as a resting base, do show a suggestion of slow component.

The alactic velocity constants for the recovery curves of the present study appear to be within the range reported by the other investigators cited above, or calculated from their data. For the fast or alactic component, the obtained mean k_1's of 1.06, $\sigma = .12$ and 1.11, $\sigma = .24$, are well within Berg's figure of 1.33, $\sigma = .31$. The k_1's from Hill's subject range from 1.10 to 1.73 and from Margaria's subject, from 1.04 to 1.66. According to Berg, the alactic velocity constant is independent of work load within fairly wide limits, as is indicated by these results.

In the case of the slow or lactic debt velocity components, there is some question as to whether the current results are comparable to those reported by other investigators. To determine precisely the absolute magnitude of these constants it is necessary to follow recovery for a period of one to two hours (11). Obviously the subjects must remain very relaxed and quiet since slight

variations in metabolic rate are important because the curves are near their asymptotes. It was not possible to observe these requirements in the present study. Even with the 35-minute recovery period that was used, most of the subjects were becoming restless near the end of the experiment and their oxygen consumption tended to rise. This would have the effect of shortening the apparent recovery time, thus increasing the magnitude of the k_2 constants and resulting in an apparent lactic debt that is smaller than the true value. There is also the possibility that breathing the oxygen-enriched air of the closed circuit system effected the recovery constants.

We have employed the terms 'alactic' and 'lactic' debt as convenient descriptive terms for the fast-component and slow-component metabolic recovery systems, but it should be kept in mind that oxygen debt recovery curves, while possibly reflecting the fundamental biochemical mechanisms, are at best only indirect measures and may in fact be considerably influenced by other factors of the physiological recovery process.

SUMMARY AND CONCLUSIONS

Nine subjects exercised on a bicycle ergometer at a constant speed of 61 pedal rpm for six minutes at two work loads—690 and 920 kg.m/min. Oxygen consumption during exercise and recovery was measured with a closed circuit apparatus. The mean net efficiency at the heavier load, 19.3 per cent, was significantly less than the 21.2 per cent efficiency found with the lighter exercise.

The metabolic recovery data were fitted with a two-component curve system of the form $y = a_1 e^{-k_1 t} + a_2 e^{-k_2 t}$. Both components increased in magnitude with the heavier work, but the change in the slow-recovery or lactic debt phase was relatively much greater, even though the amount of fast-recovery or alactic debt was well below the limit magnitude. The oxygen equivalent of the reduced efficiency, a matter of some .20 l/min., was too large to be ascribed to factors such as greater postural tension with the heavier work. Lower metabolic efficiency of the lactic debt mechanism, as compared with the alactic mechanism, was suggested as an explanation of the lowered efficiency.

Alactic velocity constants were not significantly changed by the increased work load and were within the range of magnitude reported by others or calculated from their data. The lactic velocity constants were also independent of work load, but were larger than found in experiments by others because the recovery period was only followed for 35 minutes, resulting in an underestimate of the true lactic debt.

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Influence of Age, Sex, Physique and Muscular Development on Physical Fitness

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GALLAGHER AND BROUHA (1) have pointed out that physical fitness has at least three main aspects: *a*) static fitness, which embraces an organically sound, well developed and well nourished body; *b*) functional fitness, which embraces the ability to do strenuous work; and *c*) specialized fitness, which embraces the ability of a subject to perform specific skilled tasks. Each of these three aspects also has several subdivisions. Thus, functional fitness includes the ability to perform moderate work (where a 'steady state' in respiratory and cardiovascular response is attained), the ability to perform severe muscular effort (involving the acquisition of a rapidly increasing oxygen debt), the ability to move with speed, muscular strength and, possibly, the ability to perform for prolonged periods moderate exercise to fatigue. We have studied these various subdivisions of functional fitness using some 7,000 Ceylonese subjects and the influence of age, sex, physique and muscular development on performance ability has been assessed.

METHODS

About 7,000 Ceylonese subjects from the age of 10 years upwards and of both sexes have been examined. The majority of subjects were school pupils (10 to 20 years inclusive), but the adults included workers on tea, rubber and cocoanut estates, Colombo harbor laborers, policemen, plumbago miners, university students, government clerks, Agricultural Corps personnel and peasant cultivators. Thus the major occupation groups in Ceylon were represented in the survey. The schools were chosen, after consultation with the Education Officers for each Province, as being typical of the social and economic status of each area. For adult subjects, the cooperation of estate superintendents and other labor overseers tended to determine our choice. At each place of investigation, subjects were picked by drawing names at random, a pre-determined number being chosen for each age group and sex. Our total group represented, numerically, about one-thousandth of the total population of Ceylon and this proportion was maintained for each province, occupation and economic level.

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The functional tests performed by each subject included: *a*) The *Harvard Step Test* (2), a moderate exercise test, in which a 'steady state' is reached (3). A 20-inch step was used, and 30 'step up step down' cycles per minute were performed for 5 minutes. *b*) The *Endurance Step Test* (4), a severe exercise test, in which a rapidly increasing oxygen debt is acquired and fatigue quickly ensues. Again a 20-inch step was used but, here, 45 step up and step down cycles per minute were performed until the pace could no longer be maintained. We have shown that this test distinguishes the fit from the unfit, gives repeatable assessments in the case of subjects not undergoing specialized training, and, for trained athletes, it can differentiate between those specializing in long-distance events and those specializing in running shorter distances. *c*) The *Exhaustion Step Test* which was performed by only 1,000 male subjects. It consisted of the Harvard Step Test performed by each subject for as long as possible. *d*) *Strength measurements* involved the assessment of the ability of subjects to lift a graded series of weights a definite height (20 inches) from the ground. Strength has been expressed directly as the value of the weights lifted. A second strength test has involved the measurement, by a dynamometer, of the grip of the right hand of each subject. These strength tests will note increases produced by training (5). *e*) *Speed of movement* was simply assessed by the time required to run, competitively, 100 yards.

Motivation is, of course, very important in all performance tests, and especially tests involving effort to exhaustion. For this reason, subjects usually performed our endurance step test to the vocal support of their colleagues, while the exhaustion step test was made a competition between rival schools. Similarly, all our measurements of speed were made during competitive running.

Pulse rate (in many cases heart rate by auscultation over the chest) and brachial blood pressure recordings were made by two observers before and after each step test. Indices were calculated from the formula (6): Pulse index = 100 × duration in seconds/2 × sum of pulse beats at $1–1\frac{1}{2}$, $2–2\frac{1}{2}$ and $3–3\frac{1}{2}$ minutes after exercise. Systolic blood pressure indices were obtained from: B.P. index = 100 × duration in seconds/sum of systolic B.P. readings at 1, 2 and 3 minutes after exercise. It has been shown that indices based upon the rate of recovery of the post-exercise systolic pressure can distinguish between trained and untrained for exercise fitness and that they also give repeatable assessments (4).

Taylor (7) has shown that the time run was more reliable than any of the physiological measures for assessing performance for maximal exhausting work. Therefore, additional assessments, based only upon the time in seconds of performance to fatigue, have been made for the endurance step test and the exhaustion step test.

Therefore, the following performance indices have been obtained for each

subject: *a*) moderate exercise (Harvard Step Test)—fitness index (pulse), and fitness index (B.P.); *b*) severe exercise (Endurance Step Test)—endurance index (pulse), endurance index (B.P.) and endurance index (time); *c*) prolonged moderate exercise to fatigue (Exhaustion Step Test)—exhaustion index (pulse), exhaustion index (B.P.) and exhaustion index (time). These fitness indices have each been summed, at each age and for each sex, and the mean index and the standard error of the mean have been calculated.

Measurements of height, weight and of the maximum circumferences of the arm, forearm, thigh and calf in extension were also made. These latter circumferences have been corrected for the thickness of the skin and the subcutaneous tissues (measured with calipers) so as to obtain an assessment of muscle size. An estimate of the muscular development has also been obtained by dividing these corrected circumferences by the subject's height (8).

The Ceylonese are much smaller and lighter than occidental subjects, the mean measurements at typical ages being given in APPENDIX A. Definite pubertal changes would seem to occur in Ceylonese boys between about 13 years and 9 months and 16 years. Menarche in Ceylonese girls occurs between about 13 and $15\frac{1}{2}$ years.

Estimations of vital capacity and measurements of various anthropometric characters, circumferences and lengths were also made. The bearing of these factors on physical fitness has been discussed elsewhere (5, 9).

From the physical measurements, the subjects have been classified into various physique groups or body types. In this connection we have also used the weight-height grid of Wetzel (10). Our classification has been into the following groups: *obese* (corresponding to Wetzel's channels A_4 and A_5); *stocky* (Wetzel's A_2 and A_3); *normal* (Wetzel's A_1, M_1 and A_5); *slim* (Wetzel's ' and B_3); and *undernourished* (Wetzel's channel B_4).

The mode of the temperature readings during our experiments was 82.4°F. nd the mode of the relative humidity was 76.3 per cent.

RESULTS

Moderate Exercise (Harvard Step Test)

Fitness Index (Pulse). a) Age. From table 1, it will be seen that, for males, the fitness index does not vary significantly during the pre-adolescent years but there is a sudden decline at the age of 14. (This mean index at 13 years is significantly greater than that at 14 years; $P < 0.001$.) During the male adolescent years of 14 to 16 the fitness index remains constant but less than the index for the immediate pre-adolescent years. At the age of 17 years the index declines again (the mean index at 17 years is significantly less than the mean index at 14 years; $P < 0.001$). This is followed by a steady rise in the value of the fitness index to a maximum in manhood between the ages of 21 to 25 years. Thus, the fitness index for males at 19 years is significantly greater

than that at 17 years (P <0.02) while the mean fitness index for the age group 21 to 25 years is significantly greater than the mean index at 19 years (P <0.01).

In the case of females the variation of the fitness index with age, while giving an overall picture similar to that found in males, differs in detail. There is an apparent, but not significant, decrease in the mean fitness index between the ages of 10 and 12 years. With the onset of adolescence, at the ages of 13 and 14 years, this decline becomes accelerated and significant. Thus the mean index at 13 years is less than that at 10 years (P = 0.01) and the mean index at 14 years is less than that at 13 years (P = 0.01). Just as for males, so for females, the mean fitness index between the ages of 14 to 16

TABLE 1. VARIATION OF THE MEAN FITNESS INDEX (PULSE) WITH AGE AND SEX

MALE			AGE, YR.	FEMALE		
S.E. of M. ±	No. of Subjects	Mean Index		Mean Index	No. of Subjects	S.E. of M. ±
1.06	287	87.8	10	80.4	160	0.88
1.08	298	86.6	11	79.8	162	0.89
0.92	322	87.0	12	78.3	183	1.11
0.84	340	87.4	13	77.2	160	0.84
0.87	345	81.4	14	74.3	186	0.80
1.18	260	79.3	15	72.5	150	1.32
1.10	277	79.8	16	71.9	145	1.21
1.00	242	76.0	17	76.0	82	0.92
0.97	257	78.2	18	67.8	81	2.45
1.22	161	79.8	19	76.6	40	2.74
1.08	140	82.7	20	75.0	29	2.30
0.91	406	84.4	21–25	77.0	55	3.18
1.61	239	80.2	26–30	76.9	35	5.60
1.73	119	81.6	31–35	88.0	20	3.84
2.65	77	78.1	36–40			

years does not vary significantly but, in contradistinction to the males, the mean fitness index for females at 17 years is greater than that at 16 years (P = 0.01) and that at 18 years is less than the mean index at 17 years (P = 0.001).

This decline at the age of 18 years is then followed by a steady increase in the value of the mean fitness index with increasing age to reach a maximum between the ages of 31 to 35 years. The numbers of subjects in our higher age groups for females are rather small and the variance within each group is large so that we do not stress the changes at these higher ages.

b) Sex. A study of table 1 indicates that male subjects have at most ages a significantly higher exercise fitness index (pulse) than have female subjects. Thus at the age of 10 years, the mean index for males is much higher than that for females (P <0.001). This difference is maintained until the age of

17 years when the mean value for males suddenly decreases and that for females suddenly increases so that the mean fitness index for the two sexes at this age is the same. After the age of 17 years, the mean index for females is, in general, less than that for males. For example, although the difference between the mean indices for the two sexes at 19 years is not significant, females have a lower mean index at 18 years ($P < 0.001$), at 20 years ($P < 0.001$) and for the age group 21 to 25 years ($P = 0.02$). At higher ages the sexes apparently do not differ significantly but the female groups are small in number.

c) *Physique.* We have seen that for males the mean exercise fitness index (pulse) does not vary significantly during the adolescent years of 14 to 16, the mean fitness index being more or less constant although less than the mean value in the pre-adolescent years. After the age of 16 years the mean index fluctuates for a year or two and then increases steadily to a maximum between the ages of 21 to 25 years. In comparing body types we have, therefore, taken the mean values of the fitness index for each body type for the pre-adolescent years (10 to 13 years inclusive), the adolescent years (14 to 16 years) and the optimum age group during manhood (21 to 25 years). This device, by increasing the number of subjects in each group would, we hoped, increase the significance of our results. It was not thought advisable to ignore the influence of age in comparing body types since the distribution, within each body type, of subjects between ages was not in the same proportion. An analysis of variance would be the ideal statistical method of evaluating the influence of age, body type, sex etc., but our data, being by no means homogeneous, did not lend themselves readily to this method.

A comparison of the mean fitness indices during the pre-adolescent, adolescent and adult (21 to 25 years) age groups, revealed only small differences between the various physique types (see table 2).

In the pre-adolescent and adult age groups, male or female, the mean fitness indices for each type of physique did not differ significantly. In the adolescent age group, the stocky had a lower mean index than the slim ($P < 0.05$) and the undernourished ($P = 0.05$) but the number of subjects in the stocky group was small.

On the whole physique does not appear to play an important role in determining a person's ability to perform moderate exercise.

d) *Muscular development.* The step test is an exercise involving the muscles of the lower limb. We have, therefore, measured the size of the leg muscles of our subjects in an effort to detect any correlation between muscular development and step test performance. Leg muscle development has been calculated for each subject from the following equation:

Leg muscle development = maximum circumference of thigh + maximum circumference of calf $\times$ 100/height. All measurements were made in

centimeters and allowances have been made for the thickness of the skin and subcutaneous tissues.

The actual circumference of the calf or the thigh steadily increased in our subjects from the age of 10 to the onset of manhood or womanhood; the fitness index does not increase steadily with age. The leg muscle development figures do not vary significantly from the age of 10 years to about 35 years (11).

We have calculated the coefficients of correlation (r) between thigh muscle size and fitness index pulse and between leg muscle development and fitness index pulse for 500 subjects chosen at random from our data. For thigh muscle size and fitness index $r = -0.7353$ and for leg muscle develop-

TABLE 2. VARIATION OF MEAN FITNESS INDEX WITH PHYSIQUE IN VARIOUS AGE GROUPS

PHYSIQUE	AGE GROUP, YR.	NO. OF SUBJECTS	MEAN FITNESS INDEX	S.E. OF M. ±	AGE GROUP, YR.	NO. OF SUBJECTS	MEAN FITNESS INDEX	S.E. OF M. ±
	Male				*Female*			
Obese	10–13	8	29.5	2.00	10–13	6	69.0	3.60
	14–16	9	83.4	3.04	14–16	15	68.1	4.10
	21–25	5	80.3	13.48				
Stocky	10–13	24	85.2	2.23	10–13	20	77.2	4.21
	14–16	17	76.0	2.11	14–16	49	72.2	2.35
	21–25	24	84.0	4.11				
Normal	10–13	239	88.0	0.77	10–12	205	77.9	0.81
	14–16	217	79.5	1.08	14–16	214	74.2	0.91
	21–25	155	83.4	1.41				
Slim	10–13	533	88.0	0.55	10–12	239	80.9	1.14
	14–16	378	81.4	1.02	14–16	93	73.4	1.55
	21–35	81	84.3	1.43				
Under nourished	10–13	150	87.0	0.96	10–13	44	77.8	2.53
	14–16	108	81.1	1.22	14–16	13	71.1	2.53

ment and fitness index $r = -0.8668$. These coefficients are highly significant and suggest that the less the muscular development of the individual the greater is his fitness index pulse.

Fitness Index (Blood Pressure). a) Age. Figure 1 shows the relationship between fitness index (blood pressure) and age for each sex. The relationship is markedly different from that obtained for the pulse index. Except around the ages of 19 and 20 years the blood pressure index falls steadily throughout life so that the mean index for males in their fifties is less than half that for males at the age of 10 and, for females, the mean index after 40 years is only about one-third that found at 10 years. In the case of male subjects, the mean blood pressure index does not vary significantly between the ages of 10 and 12 years; from then onward there is a steady fall. The mean index at 13 is

less than that at 10 years ($P < 0.001$), that at 14 is less than that at 13 years ($P < 0.001$), the 15-year index is less than the 14-year one ($P < 0.001$). The rate of fall seems to be accelerated at 14 years and then to slow somewhat between 16 and 20 years.

For female subjects the mean blood pressure index at 11 years is less than the index at 10 years ($P < 0.001$), that at 13 years is less than that at 12 years ($P < 0.001$) and so on. Again the rate of fall slows between the ages of 16 and 20 years.

b) *Sex.* Just as for the fitness index (pulse) so, here, we find the female subjects at most ages giving a lower mean index than the male subjects.

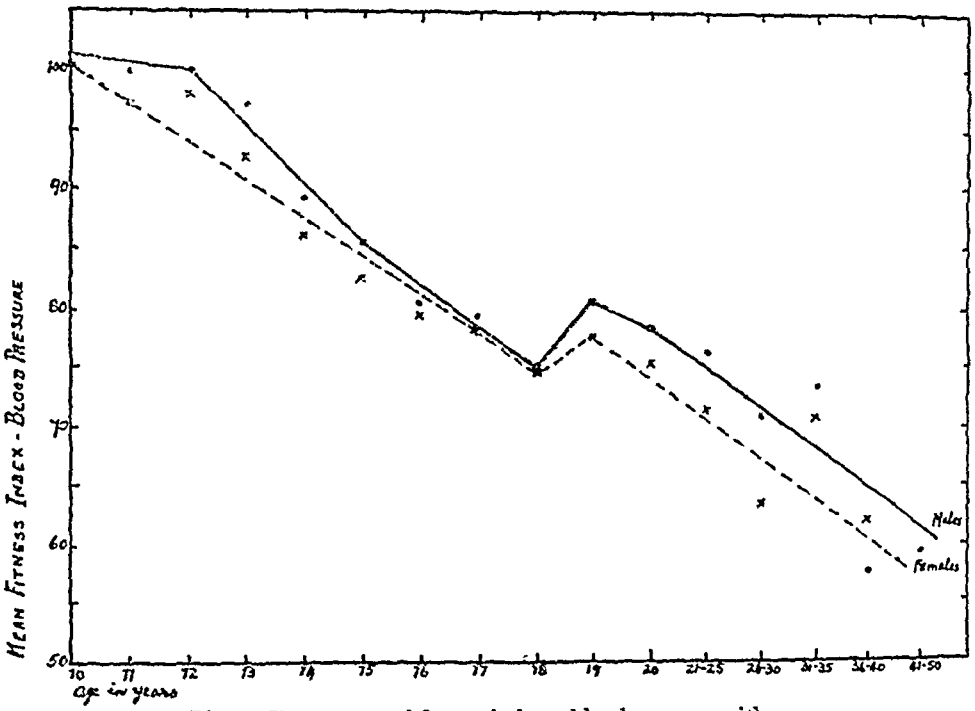

Fig. 1. VARIATION of fitness index—blood pressure with age

The index for females is less than that for males at 11 years ($P = 0.01$), at 13 years ($P = 0.001$), at 14 years ($P = 0.001$), at 15 years ($P = 0.01$), at 21 to 25 years ($P = 0.001$) and at 41 to 50 years ($P = 0.001$). Between the ages of 16 and 20 years the index for females does not differ significantly from the mean index for males.

Apparently, a man's capacity for lowering his blood pressure after moderate exercise decreases more rapidly with age than does the capacity for slowing his post-exercise heart rate.

Severe Exercise (Endurance Step Test)

Endurance Index (Pulse). a) Age. The mean endurance index (pulse) for each age and sex has been calculated. Table 3 details these mean indices and their standard errors.

There is a steady decline in the value of the mean endurance index (pulse) of females with increasing age, except for the age of 20 years. Even the rise seen at 20 years does not have a statistical significance. The onset of adolescence at the age of 14 years appears to accelerate the decrease in endurance index. For example, the decline between the ages of 10 and 13 years is not significant, but the mean index at 14 years is much less than that at 10 years (P = 0.001), that at 15 years is less than the index at 13 years (P = 0.001), and the mean index at 16 years is still lower (P = 0.001; cf. 13 years). The number of subjects in the age groups after 18 years is too small to warrant detailed analysis though the general trend in the value of the endurance index is still downward. Males show a rather similar relationship between

TABLE 3. VARIATION OF THE MEAN ENDURANCE INDEX (PULSE) WITH AGE AND SEX

MALE			AGE, YR.	FEMALE		
S.E. of M. ±	No. of Subjects	Mean Index		Mean Index	No. of Subjects	S.E. of M. ±
0.67	265	29.2	10	26.4	134	0.70
0.73	296	28.2	11	25.5	160	1.00
0.39	378	27.9	12	25.6	184	1.20
0.69	345	27.9	13	24.5	160	0.95
0.66	383	25.1	14	22.3	180	0.82
0.57	279	22.8	15	22.1	149	0.69
0.45	287	22.7	16	21.3	150	0.72
0.61	230	25.3	17	21.0	24	1.40
0.54	262	23.8	18	19.5	105	1.13
0.77	162	24.5	19	19.6	41	1.28
2.14	143	27.7	20	21.0	31	2.21
0.68	413	25.1	21–25	17.2	63	1.14
0.89	245	22.3	26–30	12.9	41	2.11
1.16	129	21.9	31–35	13.3	28	1.73
1.48	97	19.3	36–40	28.6	8	7.04
3.52	65	19.4	40–50	11.0	16	0.90

endurance index (pulse) and age. There are no significant differences between the mean indices at the ages of 10 to 13 years inclusive. At the age of 14 years the mean endurance index decreases markedly and the 15-year mean index is significantly less than that for the 14-year group (P = 0.01) so that, apparently, in males as well as in females, the onset of adolescence decreases the ability to perform severe exercise. Males, too, show a rise in the mean index at the age of 20 years though the mean index at 20 does not differ significantly from that at 19 and for the age group 21 to 25 years. This rise is followed by a steady fall in the value of the mean index with increasing age; for example, the mean index for the 26- to 30-year age group is significantly less than that for the 21- to 25-year group (P = nearly 0.01).

Unlike the female subjects, however, the male subjects give a mean index

at 17 years that is significantly higher than that for 16 years ($P = 0.001$). This contrasts with the significant fall in the value of the mean fitness index (pulse), which we have noted in the case of male subjects at the age of 17 years. In most other respects the variation of the mean fitness index (pulse) is similar to the variation with age of the mean endurance index (pulse), though the maximum value in manhood is seen at 20 years in the case of the endurance index and in the 21- to 25-year groups in respect to the fitness index, and the mean fitness index (pulse) does not vary significantly between the ages of 14 and 16.

b) Sex. The mean endurance index (pulse) at all ages is consistently less for females than the mean endurance index for males. In analyzing our data on the fitness index (pulse) we have grouped our figures for the years 10 to 13 years inclusive, 14 to 16 years inclusive and 21 to 25 years. It is convenient for purposes of comparison to use similar groupings here. Table 4 gives the mean endurance indices for these three age groups in the different sexes.

TABLE 4. VARIATION OF MEAN ENDURANCE INDEX (PULSE) WITH SEX

AGE GROUP, YR.	METHOD OF ASSESSMENT	MALE			FEMALE			SIGNIF. OF DIFF., MALE AND FEMALE
		No. of Subjects	Mean	S.E. of M. ±	No. of Subjects	Mean	S.E. of M. ±	
10–13	Endurance index	1284	28.2	0.32	638	25.5	0.49	$P = 0.001$
14–16	Endurance index	899	23.6	0.32	479	21.9	0.32	$P = 0.001$
21–25	Endurance index	413	25.1	0.67	63	17.2	1.14	$P = 0.001$

In all three age groups, the mean index for males is markedly greater than that for females.

c) Physique. Table 5 gives the mean index (pulse) for Ceylonese subjects according to their physique types. It will be seen that the slimmer or more linear the subject's physique the higher the endurance index (pulse).

The differences are more marked the older the subjects. For example, there are no significant differences between the males in the age group 10 to 13 years, but at the ages 14 to 16 years the linear types have a higher mean index than do the obese ($P = 0.05$), the stocky ($P = 0.001$), the normal ($P = 0.001$), and the undernourished ($P = 0.001$). There is, therefore, a limit to the degree of slimness since the definitely undernourished give a poor index. In the age group 21 to 25 years there are only 5 obese male Ceylonese but their mean index is significantly less than that given by the stocky ($P < 0.01$), the normal ($P < 0.01$), the slim ($P < 0.001$) and the undernourished ($P = 0.01$). This suggests that obesity may be a greater deterrant than undernourishment in determining capacity for severe exercise, but the numbers in these two groups are very small.

The female subjects do show significant differences in the younger age groups of 10 to 13 years, since the obese have a lower mean index than the stocky ($P = 0.05$), the normal ($P = 0.001$), the slim ($P = 0.001$) and the undernourished ($P = 0.02$). In the 14- to 16-year group the obese again have a lower index than the normal ($P < 0.001$), the slim ($P < 0.001$) and the undernourished ($P = 0.01$), while here, also, the stocky have a significantly smaller mean index than the normal ($P = 0.01$) and the slim ($P = 0.01$).

Therefore, physique may influence a subject's capacity for severe exercise. In addition we have noted that the variation of endurance fitness with age and sex is still seen in each physique group. The decrease of endurance with age may be due in part to alteration of physique with increasing age.

TABLE 5. VARIATION OF MEAN ENDURANCE INDEX (PULSE) WITH PHYSIQUE

AGE, YR.	PHYSIQUE	NO. OF SUB-JECTS	MEAN INDEX	S.E. OF M. ±	AGE, YR.	PHYSIQUE	NO. OF SUB-JECTS	MEAN INDEX	S.E. OF M. ±
	Male					*Female*			
10–13	Obese	9	30.5	8.54	10–13	Obese	8	17.5	2.12
	Stocky	22	26.7	3.10		Stocky	22	24.6	2.08
	Normal	341	27.9	0.86		Normal	190	26.3	0.80
	Slim	497	30.0	0.76		Slim	214	28.2	1.00
	Undernourished	145	30.9	1.32		Undernourished	52	25.2	2.09
14–16	Obese	10	21.4	3.07	14–16	Obese	17	16.8	1.54
	Stocky	15	20.4	1.73		Stocky	49	19.7	1.31
	Normal	208	23.0	0.81		Normal	208	24.1	0.74
	Slim	334	28.1	0.96		Slim	93	34.0	0.63
	Undernourished	98	21.6	0.91		Undernourished	16	20.4	2.45
21–25	Obese	5	13.9	3.55					
	Stocky	25	25.0	2.06					
	Normal	197	25.0	0.94					
	Slim	99	34.3	1.44					
	Undernourished	5	26.1	5.44					

The older the people of Ceylon become, the greater the number of people with normal or stocky types of physique. This is true for both males and females and for all the races. For example the 10- to 13-year age group has the highest proportion of slim subjects and the lowest proportion of stocky subjects; the 21- to 25-year group has the highest proportion of stocky subjects and the lowest proportion of slim subjects; the 14- to 16-year group is intermediate as regards physique distribution. (An analysis of the distribution of the subjects within the five physique types at the three age groups has been made; $X^2 = 224.5$ for males and P = much less than 0.001; $X^2 = 72.23$ for females and $P < 0.001$; see Cullumbine (11).)

Therefore, on the basis of physique alone, we should expect the capacity for severe exercise to decrease with age. This, however, is not the sole cause of the decrease because the deterioration with age is still seen even when groups of the same physique are considered.

The difference between the sexes in their capacity for severe exercise is also not due to the physique differences. Before the age of 14 years, the two sexes give a similar distribution of physique types ($X^2 = 6.212$; $P < 0.20 > 0.10$) but the capacity for severe exercise differs for the two sexes at all ages. After the age of 14 years the males are significantly less stocky than the females ($P < 0.001$) and this may then be a factor in determining the difference between the mean endurance capacities of the two sexes.

d) Muscular development. We have calculated the coefficients of correlation (r) between thigh muscle size and the endurance index and between leg

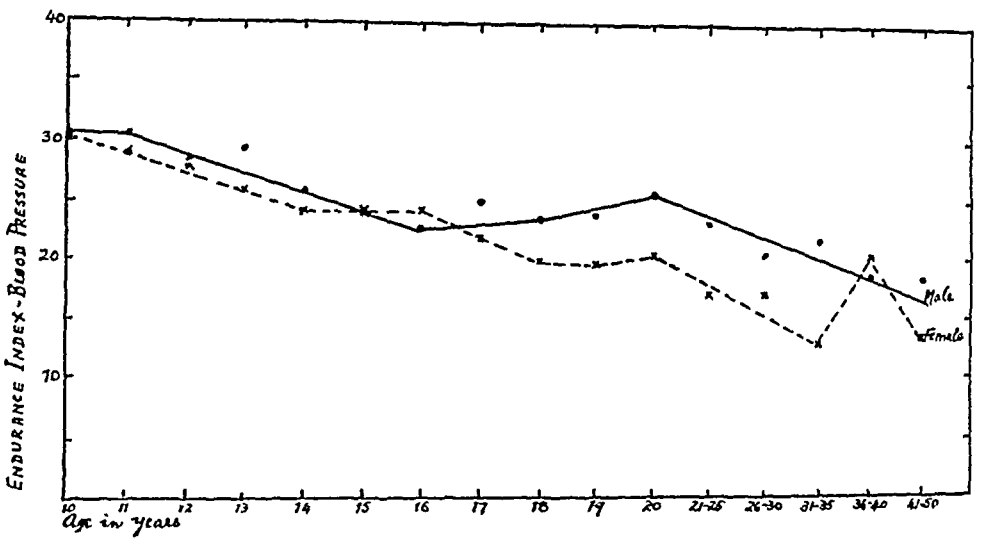

Fig. 2. VARIATION of endurance index—blood pressure with age

muscle development and the endurance index for 500 subjects chosen at random from our data. For thigh muscle size and endurance index $r = +0.1145$, a relationship which is not significant; and for leg muscle development and endurance index $r = -0.3838$, which is significant at the level of $P = 0.001$. Therefore muscular development is negatively correlated with a subject's endurance index, which is probably another way of saying that the slimmer the individual the greater his capacity for severe exercise.

Endurance Index (Blood Pressure). Figure 2 shows the relationship between the endurance index calculated from the post-exercise systolic blood pressure and age. The curves for the two sexes are very similar to those obtained when the endurance index (pulse) was related to age. When we studied the response of the same subjects to moderate exercise we found that the fitness index (blood pressure) decreased more rapidly with increasing age than did the

fitness index (pulse). Here, after severe exercise, no such marked difference between the blood pressure index and the pulse index is evident.

The variation of endurance index (blood pressure) with sex and physique is also very similar to that described for the endurance index (pulse). We should expect this similarity since we have already shown that a close relationship exists between the two indices (9).

Endurance Index (Time). The variation of endurance time with age is rather similar to that described for the endurance index (pulse) but differs a little in detail. The mean endurance time for males does not vary significantly between the ages of 10 and 13 years. Between the ages of 14 years and 16 years there is a fall in the mean endurance time (mean at 16 years less than at 14 years; $P = <0.05$), then a rise at 17 years (17-year mean significantly greater than 16-year mean; $P = 0.001$) and a further increase at the age of 20 years (mean value at 20 years greater than that at 19 years, $P = 0.01$). Thereafter the mean endurance time decreases with age, the value for the 21-

TABLE 6. VARIATION OF CAPACITY FOR PROLONGED EXERCISE WITH AGE

AGE, YR.	NO. OF SUBJECTS	TIME IN SECONDS		PULSE INDEX	
		Mean	S. E. of M. ±	Mean	S. E. of M. ±
10 & 11	194	189.4	29.4	76.7	9.0
12 & 13	204	312.9	22.4	79.5	3.7
14 & 15	208	460.3	44.0	114.4	6.9
16 & 17	206	569.2	36.5	138.8	5.5
18 to 20	188	712.7	48.7	175.3	8.8

to 25-year age group being significantly less than that at 20 years; P = nearly 0.001.

Female subjects show a more constant fall in endurance time with age. There is a slight, but insignificant, fluctuation in the mean endurance time about the age of 20 years but, otherwise, the fall is gradual and significant from the age of 10 years onward. The relationship between endurance time and sex, physique or muscular development is very similar to that noted for the endurance index (pulse).

Prolonged Moderate Exercise to Fatigue (Exhaustion Step Test), 1,000 Boys

Exhaustion Index (Pulse). a) Age. Table 6 gives the mean indices for various age groups. The capacity for prolonged muscular effort increases with age. This contrasts with our previous results in which we have noted that pre-adolescent subjects are fitter than adult subjects for both moderate and severe muscular effort.

Exhaustion Index (Time). a) Age. This method of assessment gives the same type of variation with age (see table 6).

b) Physique. Table 7 classifies the subjects according to their physique and it will be seen that those subjects with normal type of physique give the best assessment of capacity for prolonged exercise.

We have shown that the capacity for moderate exercise and for severe exercise is negatively correlated with the degree of muscular development of the legs. Calculation for the group of 1000 school boys of the coefficient of correlation (r) between their leg muscle development and the time for prolonged exercise to exhaustion gives a value of $r = -0.02911$. This is not significant and we can conclude that our data do not indicate any significant correlation between muscular development and capacity for prolonged exercise.

It is evident, therefore, that we must distinguish between rapidly fatiguing, severe exercise and more prolonged and moderate exercise to fatigue. Our main assessment has been by means of a test involving the former type of exercise because we believe that we have shown that such a test gives an accurate assessment of a subject's capacity for intense muscular effort (4).

TABLE 7. VARIATION OF CAPACITY FOR PROLONGED EXERCISE WITH PHYSIQUE

PHYSIQUE	NO. OF SUBJECTS	MEAN TIME, SEC.	S. E. OF M. ±
Obese	40	305.0	33.1
Stocky	128	360.3	27.7
Normal	278	564.2	16.8
Slim	394	521.4	22.7
Undernourished	160	359.6	25.9

Moreover, a prolonged and moderate exercise test, besides being very time-consuming, is difficult to use with any reliability on large numbers of subjects because of the great importance of motivation in determining a subject's performance. The aspect of exercise revealed by such a test must, however, always be noted in any comprehensive appraisal of the fitness for muscular exercise.

Strength

Weight Lifted. a) Age. The mean strengths and their standard errors for each age and sex are given in table 8. The mean strength of males increases with increasing age from 10 years onward until about the age of 30 years. The increase is fairly rapid until the age of 18 years, the mean strength of each age differing significantly from the previous age. For example the mean strength at 10 years is less than that at 11 years ($P = 0.02$), and that at 11 years is significantly less than the mean at 12 years ($P < 0.001$) and so on. The onset of adolescence does not appear to influence this gradual increase in

strength. After the age of 18 years the rate of increase in strength is much slower. Thus the mean at 18 years does not differ significantly from that at 19 years or at 20 years, and the difference between the mean at 20 years and that for the 21- to 25-year age group is also not significant. However the mean strength for the age group 21 to 25 years is significantly greater ($P = 0.001$) than the mean strength at 18 years so that a gradual and eventually significant increase occurs after the age of 18 years.

The strength of males appears to reach a maximum between the ages of 26 to 30 years and there is an apparent decline afterward. Actually the mean strengths for the age groups between 21 and 50 years do not vary significantly but our groups are rather small.

The increase in the strength of females with age is much more gradual than in the case of males. The mean strengths at 10 and 11 years, at 12 and

TABLE 8. VARIATION OF STRENGTH WITH AGE AND SEX

MALE			AGE, YR.	FEMALE			MALE			AGE, YR.	FEMALE		
S.E. of M. ±	Mean Strength	No. of Subjects		No. of Subjects	Mean Strength	S. E. of M. ±	S.E. of M. ±	Mean Strength	No. of Subjects		No. of Subjects	Mean Strength	S.E. of M. ±
0.450	32.8	285	10	84	31.6	0.951	1.034	68.8	250	18	86	42.4	1.378
0.480	34.4	276	11	106	33.1	0.707	1.456	69.1	138	19	48	41.8	2.198
0.560	37.4	330	12	131	35.8	0.642	1.603	71.4	122	20	24	44.0	3.470
0.618	41.1	330	13	124	36.8	1.068	0.906	74.6	280	21–25	47	44.9	2.245
0.733	44.9	325	14	161	38.9	0.784	1.095	75.7	180	26–30	31	44.3	2.775
1.034	53.2	210	15	122	41.0	0.958	1.503	74.7	125	31–35	17	48.7	1.217
0.987	59.8	280	16	120	42.4	1.039	2.047	72.9	66	36–40	4	51.0	12.329
1.257	62.0	248	17	182	40.5	1.319	2.751	74.4	30	41–50	5	47.6	5.950

Strength is measured in kg. weight lifted.

13 years and at 13 and 14 years do not differ significantly, but the mean at 11 years is less than that at 12 years ($P = 0.01$) and that at 12 years is less than the mean for 14 years ($P = 0.01$). Therefore a slow increase in strength is taking place. After the age of 16, however, strength appears to be more or less constant in females until the age of 30 years. There appears to be an increase in the 31- to 35-year group (the mean at 31 to 35 years greater than the mean at 19 years; $P = 0.01$) but this group is numerically very small.

b) *Sex.* At all the ages the strength of females is less than that of males (table 8) and the greater the age the greater the difference between the sexes. When considering fitness for moderate and severe exercise we have found it convenient to group the subjects into the age groups 10 to 13 years, 14 to 16 years and 21 to 25 years. For purposes of comparison we have used a similar procedure here. Table 9 gives the mean strength for the three age groups and

for each sex. In all these age groups the mean strength of the male subjects is significantly greater than that of the females: 10 to 13 years, $P = 0.001$; 14 to 16 years, $P = 0.001$; 21 to 25 years, $P = 0.001$.

c) Physique. The mean strengths for each physique type are shown in table 10. Statistically significant differences to be noted are:

Ceylonese males: undernourished and weaker than slim ($P < 0.001$), than normal ($P < 0.001$), than stocky ($P < 0.001$) and than obese ($P < 0.001$); slim weaker than stocky ($P < 0.001$), than normal ($P < 0.001$) and than obese ($P = 0.05$).

TABLE 9. VARIATION OF STRENGTH WITH SEX

MALE			AGE, YR.	FEMALE		
S.E. of M. ±	Mean Strength	No. of Subjects		No. of Subjects	Mean Strength	S. E. of M. ±
0.283	36.6	1221	10–13	445	34.7	0.431
0.559	52.2	816	14–16	403	40.6	0.529
0.906	74.6	280	21–25	47	44.9	2.245

Strength is measured in kg. weight lifted.

TABLE 10. VARIATION OF STRENGTH WITH PHYSIQUE, AGES 10 TO 30 YEARS INCLUSIVE

MALE			PHYSIQUE TYPE	FEMALE		
S.E. of M. ±	Mean Strength	No. of Subjects		No. of Subjects	Mean Strength	S.E. of M. ±
10.17	57.9	29	Obese	43	44.4	3.020
3.390	62.5	101	Stocky	125	41.2	0.808
0.328	61.8	911	Normal	507	39.4	0.266
0.184	51.1	1225	Slim	293	37.3	0.252
0.996	46.0	283	Undernourished	50	34.9	0.620

Strength is measured in kg. weight lifted.

Ceylonese females: undernourished weaker than stocky ($P < 0.001$), than normal ($P < 0.001$), than obese ($P < 0.001$) and than slim ($P = 0.01$); slim weaker than normal ($P = 0.01$), than stocky ($P = 0.001$) and than obese ($P = 0.001$).

Therefore, as to be expected, the thinner and the more undernourished the individual the less his strength. In the case of Ceylonese females the obese are the strongest and, in the case of Ceylonese males, the stocky and those of normal build give the highest assessment of strength. Can the difference in physique account for the differences in strength noted to exist between different ages and the two sexes?

Strength increases with age and the Ceylonese become more stocky with increasing age, but variation in physique alone cannot account for the

influence of age. This is evident if we compare subjects with the same type of physique when an increase of strength with age is still seen. Females are weaker than males but, after the age of 14 years, Ceylonese females become more stocky in build than the Ceylonese males. Therefore, again physique does not determine the difference between sexes.

d) Muscular development. The muscular development of each subject has been assessed by taking the sum of the maximum circumferences (in cm.) of the right arm and forearm and dividing by the height (in cm.) of the subject. The variation of the muscular development of the upper limb with age is shown in figure 3. There is an apparent relationship between the muscular development of the arm and the strength of each sex. The variation with age is very similar for these two properties, a maximum being reached in each instance at about 25 to 30 years in the case of males and at about 18 years in the case of female subjects.

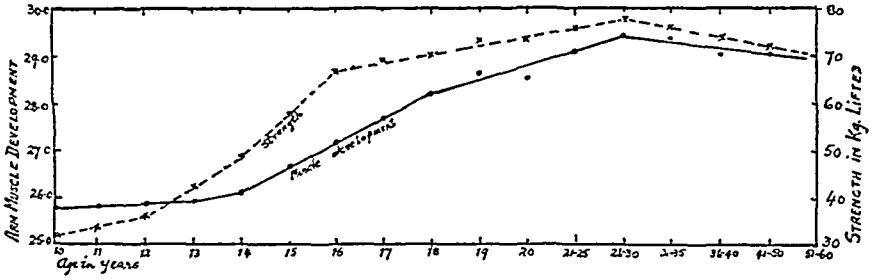

Fig. 3. VARIATION of arm muscle development and strength with age

The coefficients of correlation (r) between arm muscle size and strength and arm muscle development and strength have been calculated for 500 subjects chosen at random from our data. Arm muscle size and strength give a value of $r = +0.8324$ and arm muscle development and strength give a value of $r = +0.9124$, both coefficients are highly significant.

All the differences in strength which we have noted cannot, however, be accounted for purely by differences in muscular development. Thus, females are weaker than males at all ages, yet females have bulkier arms and forearms relative to height than have males at the ages 10 to 13 years ($P < 0.001$) and 14 to 16 years ($P = 0.001$).

Grip Strength. a) Age. The variation of intensity of grip with age is similar to that just noted for weight lifting. There is an increase from the age of 10 years onward until a maximum is reached in early manhood (about 21 to 25 years) and then a decline occurs with advancing years. It will be noted that the grip strength reaches a maximum at an earlier age than does the capacity for weight-lifting. Weight-lifting is a more complex exercise than is hand-gripping, involving as it does more joints and muscles. The difference may,

therefore, be a true one, although it is possible that there is a greater fear of strain associated with the more unnatural weight-lifting, which fact may have influenced the results.

b. Sex. The variation in the case of female subjects is again somewhat different. At all ages the intensity of the grip of females is less than that of males but the increase in grip with age parallels that occurring in males in the pre-adolescent years. From the age of 14 years onward the rate of increase in the case of females becomes much slower and an apparent maximum is reached about the age of 19 years. Grip strength also gives correlations with arm muscle size or development which are similar to those quoted for weight-lifting.

TABLE 11. VARIATION OF TIME TO RUN 100 YARDS WITH AGE, SEX AND PHYSIQUE

AGE OR PHYSIQUE	MALE			FEMALE			AGE OR PHYSIQUE	MALE			FEMALE		
	No. of Subjects	Mean Time, sec.	S.E. of M. ±	No. of Subjects	Mean Time, sec.	S.E. of M. ±		No. of Subjects	Mean Time, sec.	S.E. of M. ±	No. of Subjects	Mean Time, sec.	S.E. of M. ±
10	287	15.40	0.255	160	16.00	0.367	18	251	12.26	0.239	81	15.83	0.579
11	298	14.50	0.260	162	15.90	0.316	19	161	11.00	0.101	40	15.05	0.975
12	322	14.94	0.245	183	15.20	0.460	20	140	11.06	0.439	29	14.95	0.989
13	340	14.76	0.139	160	14.58	0.234	Obese	138	15.00	0.458	14	18.2	
14	345	13.96	0.262	186	14.21	0.283	Stocky	385	13.60	0.184	107	16.25	0.361
15	260	13.60	0.258	150	16.11	0.447	Normal	606	13.52	0.134	435	15.35	0.303
16	277	13.27	0.173	145	15.85	0.524	Slim	1294	13.73	0.130	625	14.48	0.207
17	242	12.75	0.159	82	16.25	0.274	Under-nourished	496	14.14	0.247	203	16.6	0.353

Speed

A group of schoolboys and schoolgirls were timed while running, competitively, a distance of 100 yards. Table 11 indicates the variation of this time with age, sex and physique. As was to be expected, the boys were faster than the girls and, within the age groups tested, speed of running increased with age for boys. In the case of the girls tested, speed increased with age up to 14 years, after which age there was a deterioration in performance. Boys with a normal type of physique were faster than the others and, for girls, the slim girls were the faster.

Calculation of the coefficient of correlation between leg muscle development and time to run 100 yards gives, for 500 subjects, a value of $r = +0.3873$, which has a probability of <0.001. Therefore, speed of running is correlated significantly with muscular development of the legs.

DISCUSSION

Age. Using the Harvard Step Test for the assessment of the ability to perform moderate muscular exercise we have concluded that this ability

(measured by an index based on the duration of exercise and the heart rate during recovery) is constant for boys in the pre-adolescent years, declines with the onset of adolescence, shows a further significant decrease at the age of 17 years, then rises steadily to a new maximum between the ages of 21 to 25 years, and thereafter declines slowly again. Girls behave similarly except their mean fitness index rises at the age of 17. Gallagher and Brouha (1) when testing boys between the ages of 13 and 19 years, who did a constant amount of work on a bicycle ergometer, reported that the physical fitness index was related more to body surface than to age. Johnson, Brouha and Gallagher (11), using a step test to evaluate the fitness of 609 boys ranging in age from 12 to 19 years, similarly concluded that fitness was independent of age. Our results do not conform to the conclusions of these workers and their published data do not permit a statistical analysis. For comparison our groups of subjects are greater than theirs but yet it may be that American children differ from the Ceylonese. Certainly we do not believe that our results can necessarily apply to peoples elsewhere. Other workers, however, have noted an influence of age on muscular performance. Jokl and Cluver (12), when testing South African children, noted that puberty caused a retardation in the rate of progress of the ability of boys to run 100 yards and stopped the progress in the ability of girls to run 100 yards. Espenschade (13), from observations on California boys and girls during adolescence, found that the ability for sprinting and long jumping increased in boys during adolescence but reached a maximum in girls at the age of 14 years and then tended to decline.

We have noted a decrease in the mean fitness index after early manhood and McCurdy and Larson (14), from results of similar cardiovascular tests on over 1,000 subjects between the ages of 18 and 80 years, found a decrease in efficiency in the upper age ranges and a progressive decrease in the rate of recovery of the pulse after exercise.

When assessing performance on a severe exercise test, we have concluded that the capacity to perform this type of exercise decreases with advancing age in both sexes from about the age of 14 years onward, with temporary increases at 17 years and possibly at 20 years. Jokl and Cluver (13), using the time to run 600 yards as their basis of assessment, have concluded that the 'power of endurance' of boys increases steadily between the ages of 5 and 20 years, adolescence retarding, but not interrupting, the progress. The power of endurance of girls, they found, reached a maximum at the age of 13 years and then declined so that a girl of 6 years usually had a better performance than a girl of 18 years.

The different conclusions are undoubtedly due to the different methods of assessment. The Harvard Step Test, we know, does not give a high correlation with the ability to run (16). However, most observers are agreed that the best methods of assessing fitness for severe exercise include measurement

of the time of performance of severe exercise to fatigue and the post-exercise pulse rate (7).

This decrease with age of the endurance and fitness indices does not mean that older subjects are less capable of performing muscular effort than younger people. For example, the Ceylonese boy of 18 years weighs about twice as much as the Ceylonese boy of 10 years (average weights for our subjects were 24.0 kg. at 10 years and 48.5 kg. at 18 years). Therefore, in performing a Step Test, 18-year-old subjects do twice as much work per minute as do the 10-year-old boys.

The fitness index (pulse) and the endurance indices are not correlated significantly with weight (17), but the work performed in the Step Test will be directly proportional to the weight of the subject. Another method of as-

TABLE 12. VARIATION OF MEAN WORK-PULSE INDICES WITH AGE FOR CEYLONESE MALE SUBJECTS

AGE, YR.	NO. OF SUBJECTS	HARVARD STEP TEST		NO. OF SUBJECTS	ENDURANCE STEP TEST	
		Mean Index	S.E. of M. ±		Mean Index	S.E. of M. ±
10	287	38.6	0.47	265	19.3	0.44
11	298	42.1	0.53	296	20.6	0.53
12	322	45.8	0.49	378	22.1	0.31
13	340	51.9	0.50	345	24.8	0.61
14	345	50.4	0.54	333	23.3	0.62
15	260	52.7	0.78	279	22.4	0.56
16	277	59.8	0.83	287	25.3	0.51
17	242	62.4	0.82	230	31.1	0.75
18	257	69.5	0.86	262	31.7	0.72
19	161	70.2	1.10	162	32.1	1.01
20	140	75.6	0.99	143	38.0	2.93
21–25	406	78.5	0.86	413	35.0	0.95

Work pulse index = Work done in foot-pounds/Sum of post-exercise pulse rate at 1-1½, 2-2½, 3-3½ minutes after cessation of exercise.

sessing the circulatory efficiency is, therefore, to devide the calculated work done (in ft. lbs.) during the stepping exercise by the rate of recovery of the post-exercise pulse rate, i.e. by the sum of the pulse rates at three periods during the recovery as in calculating the fitness index (pulse). Such an assessment gives the figures shown in table 12. These indices, based on work done, increase (except for the ages 14–15 years) with increasing age from 10 years to the early twenties. Therefore, when the work done is assessed, the older subjects appear to be the more efficient, but where the body weight is ignored and only the actual times of performance of a given movement by each individual are taken into account, then the younger subjects, in general, give the higher fitness indices.

Chronological age is not always the best means of classifying growing children; a grouping based upon the stage of growth or development of the child would probably be more satisfactory. One such method of grouping is by means of the 'developmental levels' on Wetzel's weight and height grid (10). We have determined the developmental level for each child and we have calculated the coefficient of correlation between the developmental level and the fitness index or the endurance time for 500 subjects chosen at random and between 10 and 20 years of age inclusive. The following values were obtained: Developmental level and fitness index (pulse), $r = -0.3403$, ($P = 0.001$); developmental level and endurance time, $r = +0.1667$ ($P = 0.1$). This means that not only is there a general tendency for the fitness index to decrease with chronological age but the index also decreases significantly with increasing developmental level. On the contrary, there is no simple relationship between developmental level and endurance time.

In contrast with the above findings, speed of movement, muscular strength and the ability to sustain moderate exercise to fatigue do increase with age to maxima in early manhood or womanhood. Similarly, speed, strength and the exhaustion indices increase with increasing developmental level and are positively and significantly correlated with the developmental level (e.g. coefficient of correlation between weight lifting and developmental level for 500 random subjects, aged 10 to 20 years, $= +0.3285$, and between handgrip and developmental level $= +0.7546$).

Sex. Metheny *et al.* (18) have compared the physiological responses and performances of men and women during and following a non-exhausting walk. In general they found that the men were fitter than the women, who had a higher pulse rate and a higher blood lactate level during the walk. They concluded, however, that there was no clear-cut division between men and women in physical fitness for exertion, since some of the best women were fitter than the poorest men. Their groups were small in number (30 men, 17 women) and they were selected subjects as to health and the amount of daily activity.

In our survey the female subjects, as groups, gave consistently lower mean fitness indices at all ages (except the anomalous 17th year and possibly the higher adult ages) than did the male subjects. Some females gave a higher index than some males but, in general, the distinction was well marked.

Similarly for severe exercise the female subjects gave consistently lower mean indices at all ages than did male subjects. Jokl and de Jongh (19), from their extensive studies in South Africa, have also concluded that women are inferior to men in endurance, though they claim that the difference in performance ability between the two sexes is not apparent till after puberty,

which merely retards development in males but may stop progress or cause a decline in females. Our data show a difference between the two sexes even in the age group 10 to 13 years. Metheny *et al.* (18) have compared the physiological responses and performances of 30 men and 17 women during and following an exhausting run. They found that the men ran twice as long, on an average, as the women before being exhausted and had higher fitness indices too. Speed and strength were also greater in male subjects than in females.

Physique and Muscular Development. Although it is commonly assumed that man's capacity for muscular exercise may be influenced by his body build there are few experimental data to illustrate this assumption. Indeed, until recently, little notice was taken in experimental human physiology of individual variations in body measurements and their possible affect on function.

On the other hand anthropometric studies do indicate that there is an interrelation between body build and capacity for exercise. Data from equal groups of negro and white American college students indicate that the negro has body measurements which should make him the more efficient in sprinting, jumping and throwing but that the white students would be superior in tests of endurance (20). Seltzer (21), from a study of 34 adult males who exercised on the treadmill while their oxygen metabolism was measured, concluded that those possessing shorter limbs, longer torsos, flatter chests and narrow hips (the 'linear' types) had a higher resting oxygen intake and a lower mechanical efficiency in moderate work. Gallagher and Brouha (1), when measuring the efficiency for hard muscular work in adolescent boys using a method in which the work was kept constant, found a closer relationship between fitness and body surface than between fitness and age, weight or height alone.

Winslow and Gagge (22) showed that, if a large man and a small man performed work on a bicycle ergometer, then their efficiencies were equal and the increase in metabolic rate was proportional to the work output and was not related to body weight. This is presumably because the subject does not have to move his body weight in order to do this type of work. Robinson (23), however, using a motor treadmill also found that the efficiencies of a large man and a small man in performing the work were the same, but under environmental conditions (32° C. and 70 per cent humidity) which limited heat dissipation, the larger man accumulated heat throughout the work and had to stop with approaching heat exhaustion, whereas the smaller man attained heat balance. This illustrates the importance of the ratio of weight to surface area because, in both men, the heat produced was in proportion to body weight but the ratio of weight to surface area was 20 per cent greater in the larger man.

Women with a muscular type of body are usually better athletes than

those with a feminine build, but Carpenter (24) believes that muscular development and strength are more important than mere body type. Pryor and Smith (25) have found that adolescent girls with a broad, lateral configuration have a greater capacity for physical work than the linear type of girl.

Our data gave no evidence that physique plays an important part in determining a person's response to moderate exercise. Our groups of subjects are numerically much larger than those of other workers and also the latter have, in many cases, used a different method of assessment. Gallagher and Brouha (1) also based their conclusions on the rate of recovery of the pulse rate, but Winslow and Gagge (22) and Robinson (23) measured the heat production and the metabolic rate; Seltzer (21) estimated the oxygen metabolism; while Jokl (8) considered the time taken to run a short distance. These various methods of assessment may not be equally sensitive or reliable. Most workers are agreed that the pulse rate during recovery from a fixed amount of submaximal or moderate work is one of the most reliable measures of fitness (1, 3, 7, 26).

As regards severe exercise, Seltzer (21) has studied the oxygen metabolism of 34 subjects while they exercised on the treadmill. He found that those with a 'linear' physique had, in exhausting work, a greater capacity per kilogram body weight for supplying oxygen to the tissues than had the 'lateral' types of individual. Jokl (8) found that 20 South African white girls in the postmenarcheal state were more bulky for their height and had a lower 'power of endurance' (measured by the time to run 600 yards) than had 20 girls in the premenarcheal state.

Our results support these observations. We have noted that those with a slim or linear type of physique have a greater capacity for severe exercise than have the stocky or the obese type. Definite undernourishment limits this advantage of linearity but obesity would seem to be more harmful than even undernourishment.

Strength, speed and performance of moderate exercise to fatigue are all greatest in these with a normal or stocky type of physique. These are the three aspects of functional fitness which also increase with age.

SUMMARY

The response to moderate and severe exercise and the strength and the speed of movement have been measured for 7,000 Ceylon subjects from the age of 10 years upward.

The fitness index (for 5 minutes of moderate exercise) and the endurance index (severe exercise) decrease with age. The fitness index also decreases with increasing developmental level, but the endurance index is not related to the developmental levels. These indices are based partly on the time of perform-

ance of a standard type and rate of exercise. If the work performed is taken into account then the older subjects give the better assessments.

Speed, strength and the ability to sustain moderate effort to exhaustion all increase with age, to reach maxima in early manhood or womanhood. These aspects of dynamic fitness also increase with increasing developmental level. In all respects female subjects give poorer assessments than do males. Those with a normal or a stocky body build have, on an average, the greatest speed, the greatest strength and the greatest ability to sustain prolonged muscular effort. Severe exercise is best performed by those with a slim body build.

Within the range presented by our group of subjects, the less the leg muscle development the greater was the fitness index and the endurance index. The greater the leg muscle development, the greater was the speed of movement. The greater the arm muscle development, the greater was the strength.

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APPENDIX A. MEAN HEIGHTS AND WEIGHTS, AND STANDARD ERRORS OF THE MEANS, FOR CEYLONESE

AGE	MEAN HEIGHTS		MEAN WEIGHTS		67% DEVELOPMENT LEVEL (WETZEL, 10)	
	Males	Females	Males	Females	Males	Females
yr.	*cm.*	*cm.*	*kg.*	*kg.*		
10	126.3 ± 0.65	125.8 ± 0.83	24.0 ± 0.40	23.9 ± 0.31	54	55
11	130.2 ± 0.53	132.0 ± 0.99	26.5 ± 0.32	27.5 ± 0.36	62	65
12	134.1 ± 0.52	135.5 ± 0.86	28.8 ± 0.31	30.1 ± 0.33	70	76
13	138.8 ± 0.85	140.6 ± 0.79	32.4 ± 0.52	33.5 ± 0.40	80	87
14	145.2 ± 0.76	143.2 ± 0.61	33.8 ± 0.35	37.4 ± 0.55	90	97.5
15	153.2 ± 0.93	145.6 ± 0.74	36.3 ± 0.54	38.2 ± 0.44	102	107
16	154.0 ± 0.89	148.7 ± 0.44	40.9 ± 0.52	39.7 ± 0.47	113	113
17	159.2 ± 0.62	150.0 ± 0.52	44.7 ± 0.49	41.5 ± 0.48	123	114
18	160.5 ± 1.41	150.4 ± 0.98	48.5 ± 0.51	44.2 ± 0.51	128	115
19	160.7 ± 1.20	149.2 ± 1.08	49.2 ± 0.58	43.5 ± 0.62	131	115.5
20	161.9 ± 0.99	149.7 ± 1.45	49.9 ± 0.46	43.2 ± 0.59	132	116
21–25	161.3 ± 0.66	149.5 ± 1.36	50.7 ± 0.30	41.1 ± 0.58	132	116

Evidence for Adrenergic Sweating in Man[1]

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IT WAS PREVIOUSLY REPORTED (1) that in the course of an investigation on the vasomotor effects of Dibenamine (*N*,*N*-dibenzyl-β-chlorethylamine hydrochloride) an adrenergic blocking agent, spontaneous palmar sweating in man was found to be blocked. The interpretation of this observation appeared to be at variance with the known concept of the strictly cholinergic innervation of these glands. From the preliminary observations it was concluded that in addition to the known cholinergic innervation of the sweat glands, there seemed to be also an adrenergic component in the nervous mechanism of sweating in man. In the present paper, further data are presented in support of the original conclusion.

METHODS AND MATERIAL

Spontaneous and locally-induced sweating by intradermal injection of various drugs was studied. A colorimetric method developed by Silverman and Powell (2), was used for determining the presence and the amount of sweating. Prints of the sweat glands were obtained on paper treated with tannic acid. The latter reacts with the iron of ferric chloride painted on the skin, to form a stain on the paper ranging from gray-blue to blue-black. The size and intensity of the resulting pattern are directly proportional to the amount of sweat secreted. This method was used in all experiments.

In the study of spontaneous sweating, in all instances, prints of the palms and occasionally those of the plantar region of the feet were taken. In conjunction with this study, measurements of skin temperature of the forehead and the upper and lower extremities were recorded in all cases. These determinations were made under basal conditions, with an environmental temperature ranging from 72° to 76°F. and a fairly constant humidity. Sweat prints and thermometric changes were recorded before and after the administration of Dibenamine. The latter was administered by the intravenous route, at the dosage of 5 mg/kg. of body weight. The method of its administration was reported in a previous publication (3).

Electrical skin resistance (E.S.R.) was measured using the neurodermometer described by Richter (4). One electrode was clipped to an ear lobe and

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electrolyte paste was used on the disc of this electrode. The E.S.R. of all the fingers and toes, using the palmar and plantar surfaces respectively, was measured before, during and after the administration of Dibenamine.

The sudomotor response of the following drugs was studied: epinephrine (Adrenalin chloride, Parke, Davis & Co.), nor-epinephrine (L-nor-epinephrine or arterenol), Isuprel (N-isopropyl-nor-epinephrine), Neo-Synephrine, acetylcholine chloride (Merck), Mecholyl (Merck). In the early stage of this investigation, epinephrine and Neo-Synephrine were given by slow intravenous infusion. Because of systemic effects coupled with irregular sudomotor responses, intravenous administration of these drugs as a means of inducing sweating was discontinued. Instead, the local effects of these drugs were studied by intradermal injection. Normal saline was used as control. The volar surface of the forearm was used in most experiments. Occasionally the palmar surface of the distal phalanx of the fingers,[2] the plantar region of the feet, the anterolateral aspect of the legs and the forehead were used also. The various drugs were used in concentrations ranging from 10^{-5} to 10^{-7}. The dose used in most injections was 0.1 cc. and was made intradermally with 26- or 27-gauge needles. Rarely the doses used were 0.2 cc. or 0.3 cc. Prints were taken every 3 minutes until the disappearance of the activity of the sweat glands.

RESULTS

I. Spontaneous Sweating: Its Inhibition By Dibenamine

Colorimetric determination. Spontaneous sweating patterns were studied in 33 subjects before and after the intravenous administration of Dibenamine. Fourteen of these subjects had hypertensive vascular disease, 12 had various peripheral vascular conditions and 7 had various neurological syndromes. At the early stage of the investigation, simple clinical observations of the suppression of sweating following Dibenamine infusion were made 8 times in 2 subjects. Sixty experiments using the colorimetric method, were made in the remaining 31 subjects. Palmar sweating patterns were studied in 55 instances, and plantar sweating patterns in 5.

According to the standards described for the rating of sweating by Silverman and Powell, the pre-Dibenamine sweating patterns in this series of 60 tests were: intense in 38 per cent, strong in 27 per cent, moderate in 23 per cent, and faint in 12 per cent. Tests after Dibenamine (fig. 1) showed that spontaneous sweating was completely or nearly completely inhibited (blank print) in 47 per cent, faint in 42 per cent, moderate in 10 per cent, and strong in 2 per cent. Concomitant measurements of skin temperature showed in almost each instance a maximum vasodilatation of the cutaneous vessels of the

[2] Painful stimuli due to the needle pricking of one finger often induced intense sweating of the entire hand, thereby invalidating the test. Only cases with local responses were selected for the study of induced sweating in the fingers.

hands and fingers (90°–94°F.). The anhidrotic effect of Dibenamine was noted towards the end of the infusion, it reached the maximum within one to 2 hours, and usually lasted about 3 to 6 hours. In 8 patients out of 31 the anhidrotic effect was noted for 18 to 24 hours after the administration of Dibenamine. If vomiting occurred as a side-effect, spontaneous sweating was usually observed. Within 15 to 30 minutes after cessation of vomiting, however, the anhidrotic effect of Dibenamine became again apparent. Mecholyl and acetylcholine tested after administration of Dibenamine showed no impairment of their sudomotor effect.

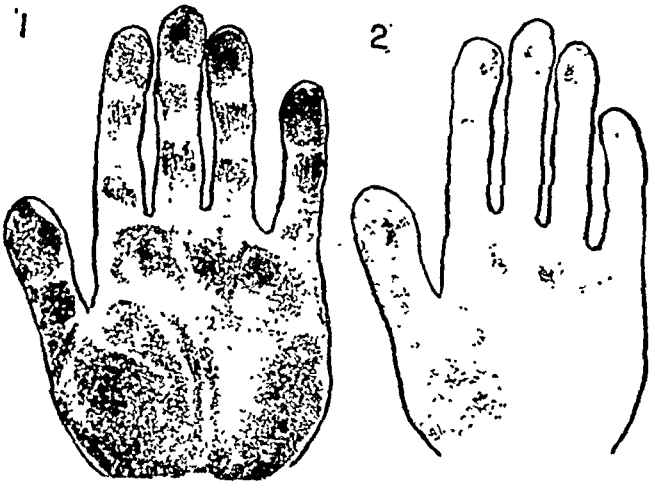

Fig. 1. PRINT OF spontaneous palmar sweating. Intense pattern before (1) and faint pattern after (2) administration of Dibenamine.

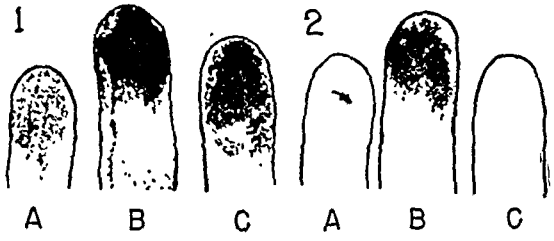

Fig. 2. PRINT OF palmar aspect of the 3 middle fingers, before (1) and after (2) administration of Dibenamine. Locally-induced sweating by intradermal injection of: *A* = 0.1 cc. saline, *B* = 0.1 cc. Mecholyl 1:500,000, *C* = 0.1 cc. epinephrine 1:1,000,000. Note in 1 the presence of both spontaneous and induced sweating patterns. In 2, after administration of Dibenamine, spontaneous sweating is completely inhibited, adrenergic sweating is abolished and only Mecholyl-induced sweating is elicited.

Electrical skin resistance (*E.S.R.*). The effects of Dibenamine on the E.S.R. were recorded 18 times in 12 patients (table 1). The average control E.S.R. in 15 experiments performed in 10 subjects was 427 K (megohms), while the average of the highest E.S.R. following Dibenamine infusion was 3682 K, an increase of 3255 K. In 3 experiments performed in 2 subjects, the post-infusion E.S.R. was too high to be read with the dermometer. The sweating responses studied colorimetrically paralleled, as a rule, the E.S.R. values.

In *experiments 1* and *4* (table 1), after having recorded the highest post-Dibenamine E.S.R., 0.65 mg. atropine sulfate was administered subcutan-

eously. Within 15 to 20 minutes the E.S.R. was too high to be read with the dermometer. It is noteworthy that control studies in the same subjects following the use of the same amount of atropine but without Dibenamine, yielded much lower E.S.R. values.

TABLE 1. ELECTRICAL SKIN RESISTANCE BEFORE AND AFTER DIBENAMINE INFUSION

PATIENT, DATE	CUTANEOUS RESISTANCE			PATIENT, DATE	CUTANEOUS RESISTANCE		
	Area[1]	Before infusion (lowest)	After infusion (highest)		Area[1]	Before infusion (lowest)	After infusion (highest)
		k	k			k	k
1. *R. A.* 4/14/18	L. palm	51	168	10. *J. B.* 10/28/48	L. 3rd finger	1800	9000
	L. 4th toe	208	594		L. 3rd toe	1285	7500
2. *R. A.* 4/19/48	L. 4th finger	277	6930	11. *I. K.* 1/31/49	R. thumb	450	2250
	L. heel	208	5200		R. 4th toe	450	3000
3. *S. R.* 4/16/48	L. thumb	336	547	12. *I. K.* 2/7/49	R. 2nd finger	900	6420
	L. heel	495	2970				
4. *B. S.* 4/23/48	L. palm	208	10400	13. *I. K.* 3/24/49	R. thumb	600	2647
	L. heel	219	1220		R. 4th toe	450	1500
5. *F. P.* 5/5/48	L. thumb	231	520	14. *M. S.* 3/28/49	R. 5th finger	600	4500
	L. 4th toe	208	1390		R. big toe	600	1285
6. *B. C.* 6/2/48	L. thumb	562	770	15. *D. A.* 4/7/49	L. thumb	450	T.H.[2]
	L. 5th toe	594	1390		L. big toe	450	T.H.
7. *R. M.* 6/9/48	L. 2nd finger	450	3750	16. *D. A.* 4/21/49	R. 2nd finger	450	T.H.
					R. 2nd toe	450	T.H.
8. *A. S.* 6/18/48	L. 2nd toe	450	3750	17. *L. G.* 5/26/49	L. thumb	500	T.H.
					L. big toe	957	T.H.
9. *J. B.* 10/25/48	L. 2nd finger	900	4500	18. *W. H.* 6/13/49	R. thumb	500	9000
	L. 2nd toe	450	6420		R. 2nd toe	450	1800

[1] The areas listed in this table were chosen as the most characteristic respones to Dibenamine.
[2] T.H. = too high values, that could not be read by the dermometer used (maximum voltage = 22.5).

II. Locally-Induced Sweating With Adrenergic Drugs

Epinephrine. Dilutions of epinephrine hydrochloride in physiological saline ranging from 10^{-6} to 10^{-7} were injected intradermally. The dose used varied from 0.1 cc. (0.1γ) to 0.3 cc. (0.3γ). The effects of epinephrine were studied in 37 subjects. The sweating response to epinephrine varied in intensity in the same subject according both to the concentration of the drug and the

area tested, and occasionally in the same subject on different days. Of the 37 subjects, 84 per cent manifested local sweating. A total of 122 tests were made, of which 81 per cent were positive. In the positive group of 31 subjects, 106 tests were made, of which 93 per cent were positive.

When sweating was induced by epinephrine, it appeared on the first print taken, i.e. within 3 minutes of the injection (fig. 2). The duration of the response ranged from 3 to 15 minutes with an average of 6 minutes. Sweating occurred in the area of vasoconstriction (pale skin). When the sweat response was marked, the sweating pattern usually followed the lymphatic spread.

Nor-epinephrine. Nor-epinephrine was used in the same dilutions as epinephrine (10^{-6} to 10^{-7}). The amounts injected ranged from 0.1 cc. (0.1γ) to 0.3 cc. (0.3γ). Sweating response to nor-epinephrine showed a somewhat wider range of variation than was noted with epinephrine. A total of 65 tests were made in 27 subjects. Of these, 74 per cent exhibited positive results. In the positive group (46 tests), the ability of nor-epinephrine to induce sweating varied with the concentration, the area tested and different days. Thus, 74 per cent were positive. Onset and duration of the response were identical to that of epinephrine. Sweating induced by nor-epinephrine, as a rule, closely paralleled the responses to epinephrine. In no instance did the former induce sweating when the latter elicited no response. The number of activated sweat glands and the amount of sweating following nor-epinephrine injection were both less remarkable than with epinephrine.

Isuprel. Of the 28 subjects tested with Isuprel (dilutions 10^{-5} to 10^{-6}), 61 per cent showed no response, 32 per cent showed a delayed (3–6 minutes after i.d. injection) and usually faint response, and only 7 per cent showed a rapid positive response. Of the total of 82 tests made, 71 per cent were negative, 25 per cent were delayed positive and only 4 per cent were positive. Isuprel-induced sweating did not last over 3 to 6 minutes, and its intensity appeared less than with the 2 preceding adrenergic agents.

Epinephrine and acetylcholine or Mecholyl. Sixty tests with Mecholyl and 18 with acetylcholine were made. All showed a positive response. Sweating due to Mecholyl was intense (fig. 2) and its duration ranged from 20 to 60 minutes. Sweating induced by acetylcholine was less intense and its duration ged from 12 to 20 minutes.

Intradermal injection of both epinephrine and acetylcholine or Mecholyl into the same point was performed in 42 instances. Concomitantly individual epinephrine, Mecholyl or acetylcholine injections were performed in adjacent areas. Analysis of the sweating patterns thus induced by the combined injections, indicates that in the first 3 minutes the intensity of the response, as a rule, appeared to be equal to the sum of the individual epinephrine and Mecholyl or acetylcholine responses. In the subsequent prints, in most cases the response appeared more intense. Its duration paralleled that of the individual

cholinergic agent used. In no instance was there even a partial inhibition of sweating as a result of the combined epinephrine-acetylcholine or Mecholyl injection.

III. Effects of Dibenamine and Sympathectomy on Adrenergic-Induced Sweating

Four subjects who had previously shown marked sweating response to intradermal epinephrine were selected for the study of the effect of Dibenamine on the adrenergic-induced sweating. Six tests with epinephrine were performed, 4 on the volar surface of the forearm and 2 on the palmar surface of the fingers preceding and following Dibenamine infusion. In all instances control tests with physiologic saline and Mecholyl were also done. One to three hours following the administration of Dibenamine, the sudomotor effect of epinephrine was completely abolished, while the response to Mecholyl remained unaffected (fig. 2). In one of these 4 subjects, after Dibenamine, intradermal injection of 0.1 cc. of atropine sulfate 10^{-5}, abolished the response to Mecholyl also.

Four subjects who had a lumbar sympathectomy (L_2 to L_4) for peripheral vascular disease were tested for pharmacologic-induced sweating. These tests were performed 4 weeks, 4 months, 5 months, and 4 years after the operation, respectively. The skin areas used were the ball of the foot and the lower half of the leg. The areas to be tested were carefully checked for completeness of denervation with the dermometer and by comparison with a symmetrical area of the other extremity. No response was obtained either with epinephrine or with Mecholyl and acetylcholine in the denervated areas.

DISCUSSION

From the foregoing data it appears that in man sweating can be inhibited by an adrenergic blocking agent and conversely that localized sweating can be elicited by adrenergic agents. These results raise the problem of the presence of an adrenergic component in the nervous mechanism of sweating in man.

The known fact that the sweat glands, although under the control of the sympathetic nervous system, respond to parasympathetic drugs, has long been a puzzle. Dale and Feldberg (5) have shown in the cat that the fibers governing these glands were cholinergic. From these observations, it was assumed by inference that the sympathetic fibers supplying the sweat glands in man were also strictly cholinergic. In support of this interpretation was the fact that in man parasympathetic drugs alone were known to promote or suppress sweat secretion. The data reported in this paper are at variance with the concept of the exclusive cholinergic innervation of the sweat glands in man.

The inhibition of spontaneous sweating induced by Dibenamine appears to be an adrenergic blocking phenomenon. All the evidence points towards a

high degree of specificity of Dibenamine. Indeed, it has been shown, both in animals (6, 7) and in man (3), that Dibenamine inhibits the pressor effect following stimulation of adrenergic fibers, and that of epinephrine. Uvnäs (8) has shown, in the cat, that Dibenamine completely abolishes the salivary secretion elicited by sympathetic stimulation, while the secretory response to chordal (cholinergic) stimulation was not abolished. As reported previously (1), myosis in man caused by the administration of Dibenamine is not reversible by epinephrine or paredrine while it is by atropine. These facts show that Dibenamine is a specific adrenolytic and sympatholytic drug. It can therefore be assumed that the suppression of spontaneous sweating by Dibenamine is truly an adrenergic blocking effect. Production of sweating by Mecholyl or acetylcholine and lack of sudomotor effect of epinephrine after Dibenamine, represent further evidence of the latter's specificity. It shows that the cholinergic component remains unaffected by Dibenamine whereas only the adrenergic is abolished.

The increased E.S.R. induced by Dibenamine is another indication that sweat secretion in man is inhibited by an adrenergic blocking agent. Although the individual E.S.R. response to Dibenamine varied, the average increase of 3255 K calculated on the basis of 15 experiments is very significant. In addition, in 3 experiments in 2 subjects the post-infusion E.S.R. values were too high to be read with the dermometer (higher than 22,500 K). The above results obtained with a quantitative procedure closely parallel those recorded with the colorimetric method.

The site of the anhidrotic action of Dibenamine appears to be peripheral. Evidence for this is furnished by two sets of experiments: 1) blockade of the cutaneous action of epinephrine, both in man (9) and animals (10), by Dibenamine introduced by ion transfer into the skin, and 2) abolition of epinephrine-induced sweating in subjects who received Dibenamine systemically, as reported in the present investigation.

The production of sweat by sympathomimetic drugs is a controversial matter. While in certain animals (horse, sheep) epinephrine induces marked sweating (11–14), in man it is known to fail to do so. However, Freund (15) introducing adrenaline by iontophoresis into the skin, found in certain cases, that the treated areas of the skin exhibited more profuse sweating than the adjacent areas while in the hot-air chamber. In addition, given systemically, ephedrine (16), benzedrine (17) and Neo-Synephrine (1) may induce sweating in man.

Although these observations may appear suggestive, the proof of direct action on the sweat glands by these sympathomimetic agents is lacking. Furthermore, the mechanism of the systemic effects of these agents is complex, and the sudomotor effects observed may be due to compensatory cholinergic phenomena. Because of these difficulties, systemic administration is not a

suitable method to demonstrate sudomotor effects of sympathomimetic agents. Indeed, at the early phase of the present investigation, epinephrine and Neo-Synephrine used by intravenous infusions, yielded irregular responses. This method was therefore abandoned, and instead direct action of adrenergic agents was then investigated by intradermal injections, a method used for the study of local cholinergic sweating (18–20). While this manuscript was in preparation, Kissin (21) and Sonnenschein (9) published reports on local sweating in man induced by subcutaneous and intradermal injection of epinephrine.

From the results obtained with this method it appears that, unlike cholinergic sweating, epinephrine-induced sweating is not universal. While 84 per cent of the subjects gave a positive response, 16 per cent failed to do so. Concentration of epinephrine, certain areas of the skin, and individual variations may possibly account for the occasional absence of adrenergic sweating. More information on this point is desirable. It is interesting to note that contrary to the common belief vasoconstriction (pale skin) induced by epinephrine is not incompatible with the secretory activity of the sweat glands. Judging from the smaller number and finer size of the dots obtained by the colorimetric test, it appears that adrenergic sweating is less intense than that obtained with acetylcholine and especially Mecholyl. The duration of its effect is shorter than that of the cholinergic sweating.

In view of the known inability of Dibenamine to block inhibitory adrenergic systems, it appeared of interest to learn: *1*) which sympathin was involved in the inhibition of sweating by this drug, and *2*) in the epinephrine-induced sweating which component of the latter was responsible for the adrenergic sweating. Nor-epinephrine and Isuprel were used individually to that effect, since, according to the available evidence, nor-epinephrine possesses the physiologic properties of sympathin E (22–24), while Isuprel exhibits those of sympathin I (25).

As shown above, nor-epinephrine induced sudomotor effects in most subjects (74%) who exhibited epinephrine sweating while Isuprel failed to do so in the majority of the cases (71%). These data seem to suggest that sympathin E or the excitatory component of epinephrine are responsible for the sudomotor ability of the adrenergic systems.

The fact that 25 per cent of the tests with Isuprel showed delayed positive response may be difficult to reconcile with the above interpretation, but it is possible to assume tentatively that hydrolysis of Isuprel in the skin yields nor-epinephrine which is ultimately responsible for the sudomotor effect.

The results obtained with simultaneous injection of epinephrine and acetylcholine or Mecholyl into the same point indicate that these agents exhibit a synergistic sudomotor action. These data show that the secretory activity of the sweat glands, as in the case of the salivary glands, is augmented both by cholinergic and adrenergic stimulation.

The problem of a qualitative difference of the two types of sweating was not investigated. However, that such a difference might exist is suggested by the known fact that sweat in anxiety is thick and sticky in contradistinction to the watery character of sweat which is caused by heat. The only common factor noted in this work between adrenergic sweating and sweat in anxiety is that both occur in a skin with a poor blood supply.

Failure of sweat response to epinephrine and Mecholyl or acetylcholine in sympathectomized areas is a finding difficult to explain. Evidence has been presented for the direct action of cholinergic agents on the sweat glands. The fact that neither cholinergic nor adrenergic sweating could be evoked in the denervated areas suggests a different mode of action or possibly early degenerative changes of the sweat glands after sympathectomy.

SUMMARY

Spontaneous sweating in man was found to be blocked by Dibenamine, an adrenergic blocking agent. The anhidrotic effect of this drug was determined both by a colorimetric method and by the electrical skin resistance. Production of sweat by adrenergic drugs was studied by intravenous and intradermal injections. Systemic administration was not a suitable method to demonstrate sudomotor effects of sympathomimetic drugs. Intradermal epinephrine produced sweating in 84 per cent of the subjects. Its sudomotor effect was inhibited by Dibenamine in all cases.

Tests performed with nor-epinephrine and Isuprel suggest that sympathin E and the excitatory component of epinephrine are responsible for the sudomotor ability of the adrenergic systems. Results obtained with intradermal injection of both epinephrine and acetylcholine or Mecholyl into the same point indicate that the secretory activity of the sweat glands is augmented both by cholinergic and adrenergic stimulation. These agents exert therefore a synergistic sudomotor action.

Since sweating in man can be elicited by adrenergic agents and inhibited by an adrenergic blocking agent, it is concluded that, in addition to the known cholinergic fibers supplying the sweat glands, there is also an adrenergic component in the nervous mechanism of sweating in man.

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Determination of Renal Clearance of Radioiodine

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AS A PART of a continuing program of observation concerned with the metabolism of radioiodine, we have used the equational relationships developed, to calculate quantities related to renal function. The general principles employed have been used by others for chemically analyzed substances utilized in clinical tests (1–3). We have made specific use of the observations obtainable with radioactive iodine, in conditions where not all of the substance was being excreted in the urine (unusual for clearance calculations), have advanced a method for using the curve of urine content as well as the curve of blood concentration, and have compared the results obtained by using these methods with a more usual method for estimating clearance.

DIRECT CALCULATION OF CLEARANCE

The methods used for determination of amounts of radioactive iodine in the blood and urine have been previously described (4). Clearance, calculated directly, is obtained by observing the rate of excretion into the urine during a period of time, and dividing this quantity by the blood concentration during that period.

$$Cl = \frac{U_2 - U_1}{\bar{P}(t_2 - t_1)},$$

where U_2 and U_1 are the total quantities of radioiodine (I^{131}) that have been excreted into the urine up to times t_2 and t_1 respectively, and P is the concentration of I^{131} in the blood plasma in the period $t_2 - t_1$.

Since, in the present situation, the concentration of radioiodine in the blood is changing, we must use for P the mean concentration $\bar{P}$. As will be shown later, in the period of observation the blood concentration is decreasing exponentially, and under these circumstances, the mean value $\bar{P}$ for the period from t_1 to t_2 is given by

$$\bar{P} = \frac{P_1 - P_2}{\ln P_1 - \ln P_2}$$

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where P_1 and P_2 are the concentrations at t_1 and t_2 respectively and ln P_1 and ln P_2 are their natural logarithms. In practice, the observed concentration at the midpoint between t_1 and t_2 is a sufficiently good approximation of $\bar{P}$.

DETERMINATION OF CLEARANCE FROM THE PARAMETERS OF THE FITTED CURVES

The relations of the quantities concerned here, and their changes with time during the course of observation, can be expressed with close approximation according to a simplified model as follows:

Consider the hypothetical case, in which the ingested I^{131} is immediately absorbed and thoroughly mixed in a 'compartment' of extracellular fluid, and that the concentration in the plasma, P, represents the concentration throughout the compartment.[1] Assume that, for a period afterward, the I^{131} passes from the plasma through the kidneys to the bladder, and to the thyroid, and to other organs and tissues, and that the return from these to the plasma, as well as other interchanges of I^{131}, is small in amount, and may be neglected. Assume that the quantity transferred from the plasma to any particular tissue, in a short time, is proportional to the quantity in the plasma. Represent the amount of I^{131} in the urine as U, the amount in the thyroid as T, the amount in any other tissue as O, the amount in the plasma as I.

$$dU = r_U I\, dt \tag{1}$$

$$dT = r_T I\, dt \tag{2}$$

$$dO = r_O I\, dt \tag{3}$$

The amount leaving the plasma will be the sum of the amounts transferred

$$dI = -(dU + dT + dO) = -r I\, dt \tag{4}$$

where r_U, r_T, r_O are characteristic proportionality constants, and $r = r_U + r_T + r_O$.

Integrating (4) we have: $I = I_0\, e^{-rt}$ (5)

Dividing by V_{P_1} the plasma volume,

$$P = P_0\, e^{-rt} \tag{6}$$

Integrating (1) with substitution of (5) for I, we have

$$U = U_f\,(1 - e^{-rt}) \tag{7}$$

where the previously mentioned symbols are as defined, $P = I/V_P$ is the concentration in the plasma, I_0 and P_0 are the values for $t = 0$, U_f is the final asymptotic amount of U, and is equal to $\frac{Pu}{P} I_0$.

[1] We are employing the terminology of reference 3.

By definition, clearance is the absolute rate of change of amount in the urine, divided by the blood concentration.

$$Cl = \frac{dU}{dtP} = \frac{U_f}{P_0} r \tag{8}$$

If, as is the fact, absorption and thorough mixing do not take place immediately, but require a time, say t_1, then essentially the relations (5), (6) and (7) will hold after t_1. Represent the values of P, U at time t_1, under the hypothetical conditions of instantaneous absorption, as P_1, U_1; and under the delayed conditions, as P_1', U_1'. The relations under the modified conditions, in the period following t_1, will then be given by

$$I = I_0' e^{-rt} \tag{5a}$$

$$P = P_0' e^{-rt} \tag{6a}$$

$$U = U_f' (1 - e^{-rt}) + U_0' \tag{7a}$$

where

$$I_0' = I_0 \frac{P_1'}{P_1}, \qquad P_0' = P_0 \frac{P_1'}{P_1}$$

$$U_f' = U_f \frac{P_1'}{P_1} + U_0'$$

$$U_0' = U_1' - U_1$$

According to (6a), if absorption of I^{131} into the plasma, and its transmission from the plasma, during the interval to t_1, are such that at t_1 the value of P is P_1', rather than P_1 (which it would have been with instantaneous mixing), then the blood curve after t_1 is a decreasing exponential function, which, extrapolated back to $t = 0$, crosses the P axis at a value P_0', and this bears the same ratio to P_0 (the value for instantaneous mixture), as P_1' does to P_1. The urine curve (7a) U will be an increasing exponential function after t_1, which, extrapolated back to $t = 0$, crosses the U axis at U_0' instead of at zero (which is the value for instantaneous mixing). The value of U_0' will depend on what was the value of U at t_1, that is, on U_1'. This, in turn, will depend on the average blood concentration during the period up to t_1. If the average blood concentration, during that interval, was the same, in the delayed conditions, as the average for the situation with immediate absorption, then the amount of I^{131} which has passed into the urine during the interval, will also have been the same; $U_1' = U_1$ and $U_0' = 0$. On the basis of independent observations, and also from study of relation (7a) with the observations of this investigation, to be described later, we have concluded that this is substantially the case, and we therefore have taken U_0' as equal to zero. We have, then

$$U = U_f' (1 - e^{-rt}) \tag{7b}$$

where $$U_f' = U_f \frac{P_1'}{P_1}$$

This (*7b*) means that the urine curve U, after t_1, is an increasing exponential function, rising toward an asymptote, U_f', which bears the same ratio to U_f (the asymptotic value of U for instantaneous mixture) as P_1' does to P_1. From (*8*), (*6a*) and (*7b*) we have for clearance

$$Cl = \frac{U_f}{P_0} r = \frac{U_f'}{P_0'} r \tag{8a}$$

It is seen, then, that the fact that there has not been instantaneous mixing does not invalidate using the observations after mixing has occurred, and extrapolating, though the extrapolation gives P_0' instead of P_0, and U_f' instead of U_f. It is relation (*8a*) from which clearance is estimated.

The quantities r, U_f' and P_0' required for the evaluation of (*8a*) can be estimated in different ways. The most technically 'correct' method is to fit (*6a*) and (*7b*) simultaneously, by least squares. This requires an elaborate and rather difficult calculation. The values P_0' and r can be estimated from the blood curve of P, and independently the values of U_f' and r can be determined from the urine curve of U. Since r is the same for (*6a*) and (*7b*), this will raise a problem of reconciling the two independent estimates of r (though these will generally be quite close). Because we consider the evaluation of r from the blood curve to be the best, and for reasons of comparative ease of calculation the following method has been adopted.

It is to be noted that (*6a*) and (*7b*)—giving respectively, the concentration in the blood, and the amount of iodide in the urine, at time t—are exponential functions, the first decreasing to zero and the second increasing toward an asymptotic value U_f', but both having the same exponential rate constant r.

From (*6a*) we have $$\log P = \log P_0' - (r \log e)\, t \tag{9}$$

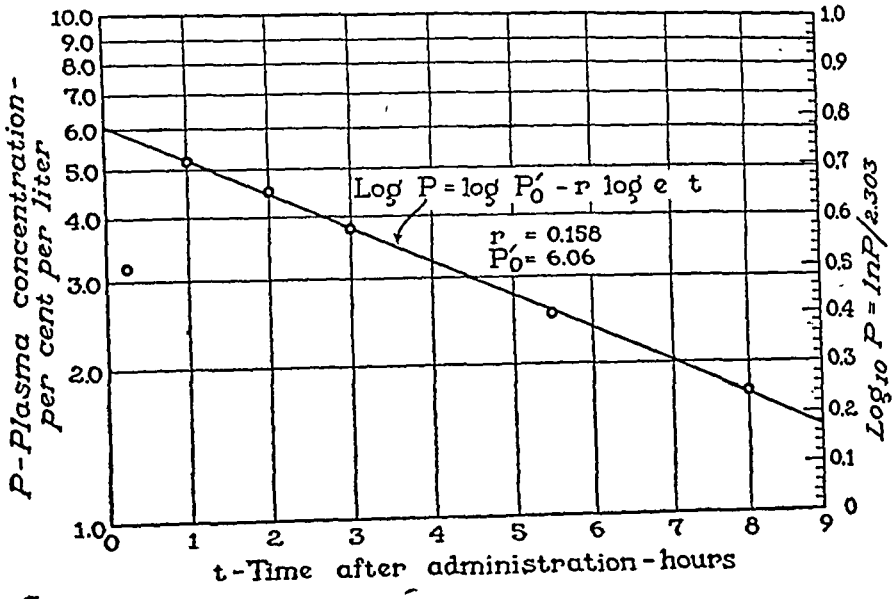
By plotting $\log P$ against t (or P against t on semilog paper) a straight line relation should be obtained; from the slope, r can be evaluated, and from the intercept at $t = 0$, P_0' can be evaluated.

With r thus determined, we proceed to the estimation of U_f' as follows: It is to be noted that equation (*7b*), giving the exponential curve of increasing values of U in the urine, contains r, which has just been determined. If, using this value of r, we calculate the quantity $1 - e^{-rt}$ for each observation,[2] and

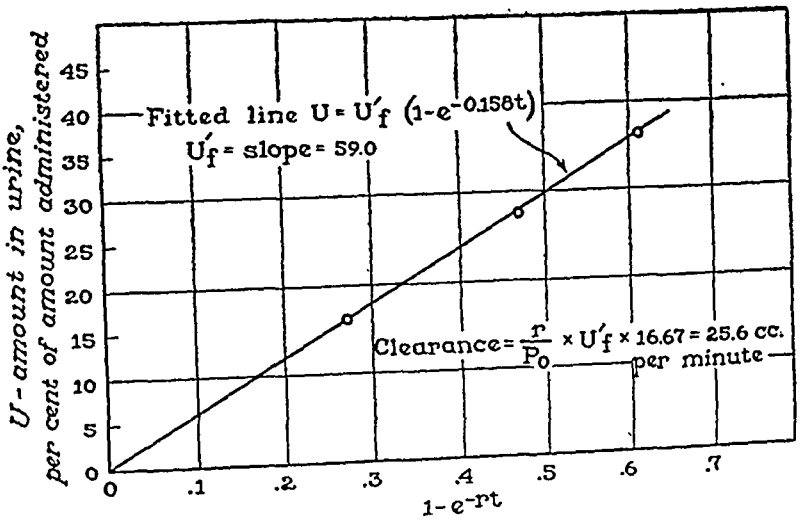
[2] A table of the values of the quantity $1\text{-}e^{-rt}$ for values of rt has been prepared and deposited with American Documentation Institute. For detailed material supplementary to this article order Document 2757 from American Documentation Institute, 1719 N Street, N. W., Washington 6, D. C., remitting $0.50 for microfilm (images 1 inch high on standard 35 mm. motion picture film) or $0.50 for photocopies (6 x 8 inches) readable without optical aid. Copies of the table, while the supply lasts, may also be obtained by writing to Dr. Joseph Berkson, Mayo Clinic, Rochester, Minnesota.

TABLE I. CALCULATION OF RENAL CLEARANCE

OBSERVED				CALCULATED	
t	P	t	U	rt	$1-e^{-rt}$
0.5	3.18	2	16.0	.316	.271
1	5.14	4	27.5	.632	.468
2	4.48	6	36.2	.948	.612
3	3.76				
5.5	2.51				
8	1.73				



a



b

Fig. 1. *a*) Log P is plotted against t, or P against t on semilog paper. The slope × 2.303 gives r. The value of P_0' is obtained as the intercept at $t = 0$. In the present example the equation $P = P_0'e^{-rt}$ was fitted by least squares, omitting the observation at the half-hour, but a graphic fit by eye of the plot of log P against t is generally satisfactory. *b*) With r determined by 1*a*, the quantity $1-e^{-rt}$ is evaluated corresponding to each t for which U has been observed. The observed U is plotted against $1-e^{-rt}$ and a line passing through the origin is fitted to the plotted points. In the present example the line was determined by least squares, but a graphic fit by eye is generally satisfactory. The slope of this line is U_f', which taken together with r and P_0' evaluated in *a*, gives clearance in accordance with formula (8*a*).

plot this against U, then according to (7*b*), a straight line passing through the origin should result, with slope U_f. Such a plot, therefore, can test whether the model used is reasonably valid, and at the same time serve to evaluate U_f' from the slope of the line. With U_f' thus determined, and r and P_0' having been obtained from the plot of (9), clearance is estimated by formula (8*a*). An example of the calculations is given in table 1 and figure 1. In figure 2 are shown

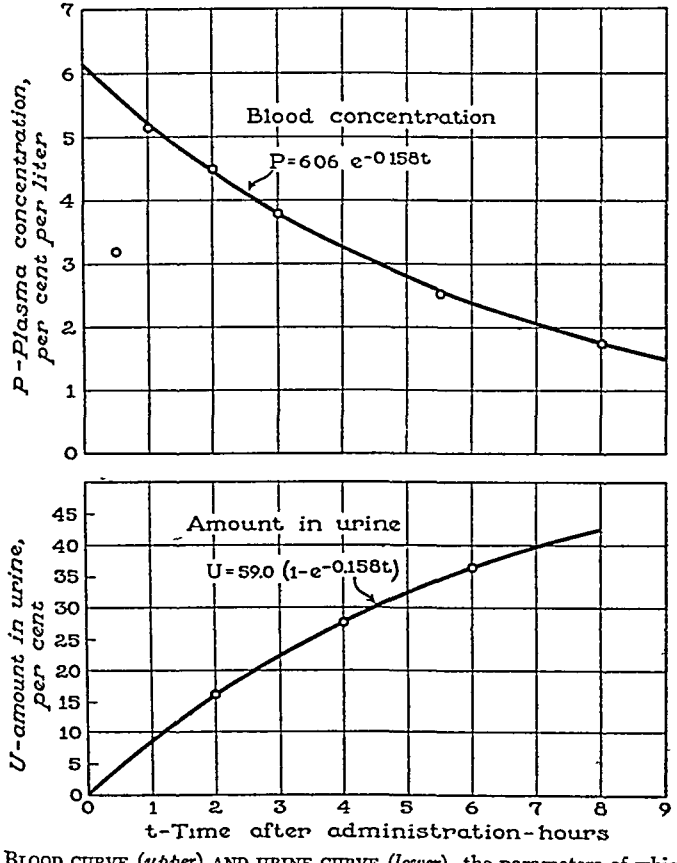


Fig. 2. BLOOD CURVE (*upper*) AND URINE CURVE (*lower*), the parameters of which were determined by the method given in the text. The circles are the observations; note the excellent agreement and the fact that the exponential rate constant of the blood curve applies also to the urine curve, even though only a fraction (r_u/r) of the blood content is being delivered to the urine.

the blood curve and the urine curve which are defined by the evaluated parameters, together with the actual observations.

It was found that, generally, in the period between one hour and ten hours after administration of the radioiodine, the observations plotted for (9), the log plasma concentration curve, show substantially linear form, in conformity with the model. Frequently, in the first hour, the observed points do not fall

on the same line as the points which follow, indicating incomplete absorption and mixing in the blood, and after about ten hours, return of the radioiodine to the blood from the tissues, and excretion of this into the urine, are of sufficient magnitude to disturb these linear relations substantially. Hence, in the studies reported here, we limited ourselves to observations in the period between one and ten hours after administration of the radioiodine. In some cases —for example, with hyperthyroidism—the time during which the relations hold substantially may be even more limited.

Calculations of the clearance by the parametric method as outlined were made for 40 patients, including euthyroid, hyperthyroid and hypothyroid cases. For each of these the clearance also was calculated directly from the observations at two points of time, by dividing the difference of U at these points by the elapsed time, to determine the rate of excretion into the urine

TABLE 2. COMPARION OF CLEARANCE CALCULATED BY TWO METHODS

CASE	CLEARANCE		CASE	CLEARANCE		CASE	CLEARANCE		CASE	CLEARANCE	
	Para-metric	Direct		Para-metric	Direct		Para-metric	Direct		Para-metric	Direct
1	19.4	22.0	11	22.9	24.5	21	31.8	27.0	31	37.9	40.5
2	12.1	12.8	12	23.1	23.8	22	32.2	34.8	32	38.6	35.2
3	13.1	13.3	13	23.8	17.2	23	33.7	30.5	33	38.7	39.2
4	15.7	16.7	14	24.9	26.0	24	33.9	37.0	34	39.6	40.5
5	17.4	20.7	15	25.6	25.5	25	34.3	37.8	35	40.7	36.8
6	18.6	20.3	16	26.5	26.7	26	34.4	35.0	36	41.2	42.3
7	20.8	21.5	17	27.1	25.5	27	34.8	34.8	37	42.9	38.3
8	21.9	23.2	18	28.9	29.3	28	36.7	29.5	38	48.7	50.0
9	22.4	27.7	19	29.8	38.5	29	37.3	36.3	39	51.9	49.2
10	22.4	41.8	20	30.9	31.3	30	37.4	46.5	40	55.6	58.3
									Mean	30.7	31.7

during this period, and dividing this rate by the blood concentration observed at the middle of the time interval. The comparison of the values of clearance as estimated by the two methods, for these cases, is shown in table 2. It is seen that the agreement is usually, but not always, close. This gives support to the general soundness of the model used. Thus the complicated dynamics of the metabolism of radioiodine can, at least under some circumstances, be formulated in a simple mathematical model that is well supported by the observations. As regards calculations, since the parametric determinations embrace a series of observations which have been graduated, while the *ad hoc* procedure uses only a portion of these, the parametric determinations are to be considered better than the direct determinations. One sees in the investigative studies on radioactive isotopes situations in which many observations are available but are not systematically utilized, and for these the method pro-

vided here will perhaps be found useful. Moreover while executing the graphic determinations one has the opportunity, at the same time, to judge whether the process conforms to a basic pattern, departures from which may in themselves be significant.

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Study of Thermocouples as Skin Thermometers[1]

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IN PREVIOUS STUDIES (1, 2) it was shown that of various skin thermometers now in use, the radiometric type of instrument gave the most dependable readings (± 0.1°C.) under various test conditions. In the more recent study (2) a heated cylindrical leather surface 12 inches x 12 inches in area was employed as the standard surface of known temperature against which the skin thermometers were tested. The experimental conditions in the tests included forced convection as well as infrared and visible radiation directed onto the surface.

Living skin has greater elasticity and is more easily deformed than the leather surface. Also, skin, with its vascular bed, presents an entirely different thermal situation from the uniform thermal gradient in an inert leather mass. It is not safe, therefore, to assume that the performance of instruments which depend upon contact with the surface for their temperature readings would be the same on skin as on the leather surface. After having established the dependability of the radiometer as regards measurement of surface temperature, the possibility was provided of studying the other types of surface thermometers on skin by comparison with the radiometer.

Of the skin thermometers previously studied, the bare wire thermocouples most nearly approached the accuracy of the radiometer when tested against the leather surface. For this reason and because these instruments are in general use for measuring skin temperature, they were selected for study in comparison with the radiometer on the normal skin. Pennes (3) has reported recently a study of this nature in which he finds agreement within ± 0.2°C. between the radiometer and thermocouple readings on the arm. To avoid the

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difficulty of comparing the radiometer, which measures an average temperature within a circle 4 cm. in diameter with the single point read by the thermocouple, Pennes measured several points within this area on the arm.

In the present study the following questions were investigated: 1) Does the contact pressure affect the skin temperature in the region of the thermocouple? 2) Does the thermocouple faithfully follow local skin temperature changes during irradiation of the skin by infrared radiation? 3) Under various laboratory conditions how do the radiometer and the thermocouples compare as regards the measurement of average temperature of the body surface?

EFFECT OF THERMOCOUPLE CONTACT PRESSURE UPON LOCAL SKIN TEMPERATURE

The no. 28 and no. 40 gauge bare junction thermocouples were selected for this study. The first method employed to vary the contact pressure was to hang the thermocouple over the forearm as shown in figure 1. The lead wires were taped to one side of the forearm and a weight of 10 gm. was attached to a supporting wire which hung down from the thermojunction on the opposite side of the forearm. The thermocouple and radiometer readings were taken at the time of imposition of this weight, and at 2-minute intervals thereafter. The radiometer was held directly over the thermocouple junction in taking readings with this instrument. By attaching additional weights up to 150 gm., the pressure of the thermocouple on the skin was increased from time to time during the course of each experiment while the temperature readings were continued. In some experiments 2 thermocouples were placed on the skin about one cm. from each other within the area observed by the radiometer. In these experiments a constant weight was maintained on one of the thermocouples while the weights were increased on the other thermocouple. The readings of the thermocouples and the radiometer were taken at 2- or 3-minute intervals as before.

Fig. 1. WEIGHTED THERMOCOUPLE METHOD for controlled contact pressure.

The pressure produced by the 10-gm. weight did not cause creasing of the skin; however, neither did it result in stable temperature readings. On imposition of this weight the temperature rose and continued to rise thereafter. The effect became more pronounced as the weights were increased. Figure 2 shows typical curves for temperature rise on weighting of the no. 28 and no. 40 gauge thermocouples compared with the radiometer reading of the temperature of the area enclosing the thermocouples. *Curve 1* represents the no. 28 gauge thermocouple readings. *Curve 2* shows temperature rise on increased weighting of

the no. 28 gauge thermocouple while a weight of 10 gm. was maintained on a no. 40 gauge thermocouple separated from the no. 28 gauge thermocouple by about one cm., both enclosed in the area observed by the radiometer. *Curve 3* shows the effect of increased weighting of the no. 40 gauge thermocouple while a weight of 10 gm. was maintained on the no. 28 gauge thermocouple which

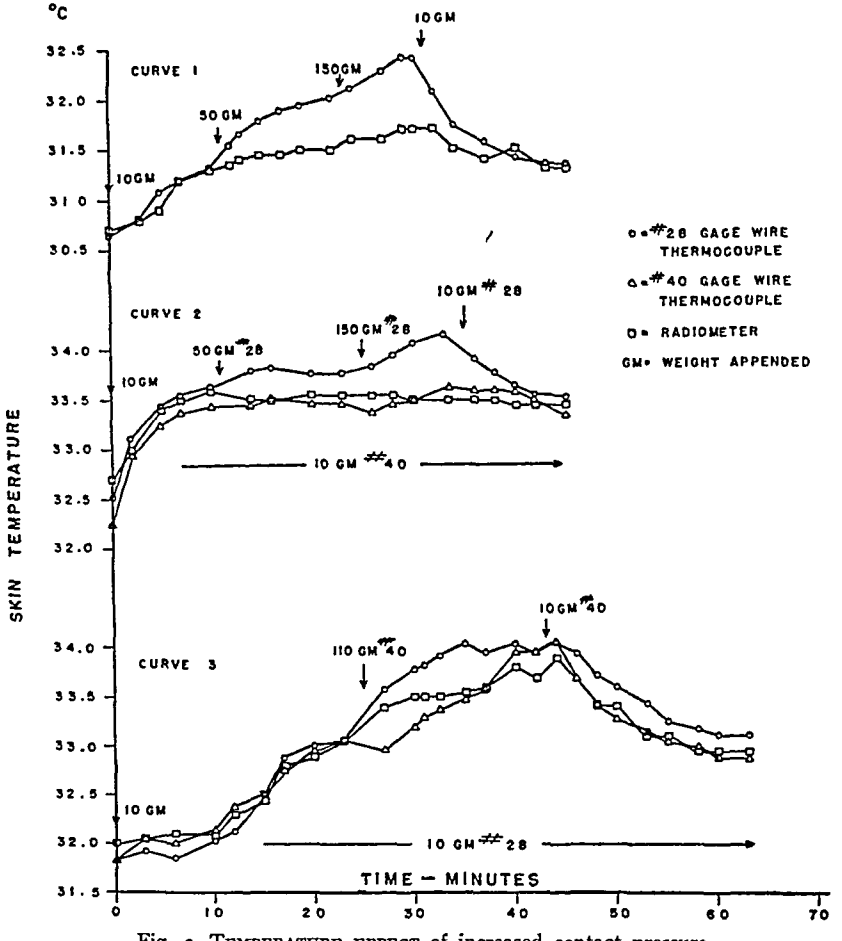

Fig. 2. TEMPERATURE EFFECT of increased contact pressure.

was separated from the other by about one cm., both being enclosed in the area measured by the radiometer. In all of these curves it is seen that the temperature rose continuously from zero time, when the 10-gm. weight was imposed, and increased with each increase in weight, dropping only on removal of the weight. In *curve 3*, although the weight was increased only on the no. 40 gauge thermocouple the temperature of the surrounding area was markedly affected as shown by the reading of the no. 28 gauge thermocouple and the

radiometer. The 110-gm. weight on this fine wire caused marked creasing of the skin and inflammation which spread to about 3 mm. on either side of the wire. It was obvious that this system interfered seriously with the blood supply to the region under observation, and induced a local hyperemia due to injury.

Since in the above described method the force was exerted over a relatively large area (*ca.* 81 mm.^{2}), a new method was employed whereby the contact area was reduced to about one-tenth of this size. The device employed (fig. 3) also provided a means of more accurately determining the effective pressure. It consisted of a lucite lever suspended over a pivot bar, and bent at angles such that weights, hung down perpendicularly from one arm, resulted in a measurable force exerted in a horizontal direction by the opposing arm.

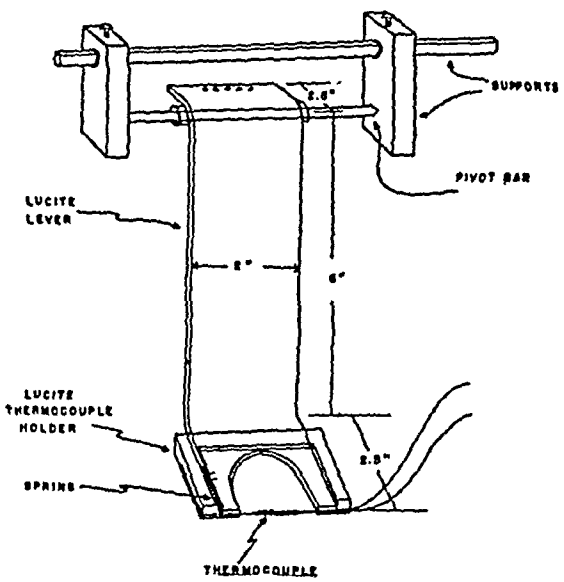

FIG. 3. LEVER DEVICE for application of thermocouple with controlled contact pressure.

This latter arm was notched out to a depth of about 1 3/8 inches. Over it was affixed a lucite frame to which the thermocouple was firmly attached by sinking it into the lucite with a heated spatula. A spring fixed between the lever and the frame spread the arms and thus drew the thermocouple taut so that it resembled in principle the fine wire thermocouple described by Henriques (4). The frame was counterbalanced and the ratio of the lever load to the force exerted by the thermocouple was determined by calibration of the apparatus against a spring gauge. The area covered by the thermocouple was about 9 mm.^{2}

For determining the effect of contact pressure with this apparatus, the unloaded lever was suspended above the head of the subject so that the thermocouple just touched the subject's forehead, zero pressure. Appropriate weights were then loaded on the lever so that a known pressure was exerted by the thermocouple on the forehead. Thermocouple readings were taken at frequent intervals from the time of contact, through the period of increased

contact pressures and for about 10 minutes after a return to minimal contact pressure.

With this apparatus it was found that on the forehead a contact force of 20 gm. (equivalent to 165 mm. Hg) was found necessary to obtain a constant temperature reading. This amount of pressure caused a rise in temperature of approximately 2°C. over the average temperature under minimal pressure. These findings are in agreement with those of a previous investigation by Remizov using a spring plunger device of his own design (5).

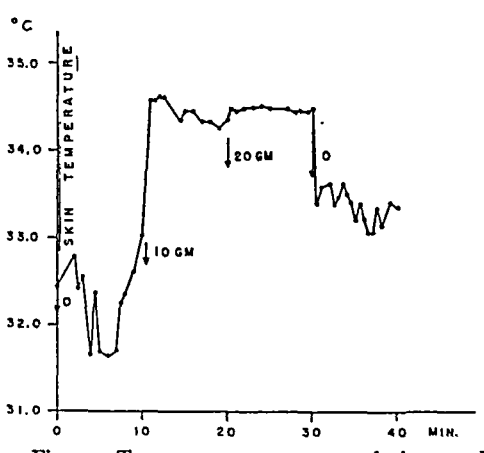

Fig. 4. TEMPERATURE EFFECT of increased contact pressure.

Figure 4 shows a typical curve of the temperature effect elicited by pressures applied by the lever system. When the thermocouple was just touching the forehead ('zero' contact pressure) the readings varied about ±0.5°C. On imposition of weights sufficient to produce a contact pressure of 10 gm/9 mm.² (about 1.1 gm/mm.²) the temperature rose sharply about 1.5°C. Thereafter it fell slowly, fluctuating about ±0.1°C. as it dropped. On increasing the contact pressure to 20 gm/9 mm.² (about 2.2 gm/mm.²) the temperature rose immediately to a level where it was maintained constant within ±0.04°C. On removal of the pressure the temperature immediately dropped a full degree Centigrade and thereafter resumed the fluctuations under zero pressure observed previously. The skin was creased from the pressure of the thermojunction and inflammation marked the site of contact after removal of the thermocouple. No spread of inflammation to the surrounding area was observed.

Comment

These observations indicated that *1*) minimal pressure of the thermocouple on the skin resulted in variable readings of skin temperature; *2*) contact pressures intermediate between 0 and about 2.2 gm/mm.² resulted in progressively greater skin temperature elevations; *3*) contact pressure of about 2.2 gm/mm.² resulted in a constant temperature reading at a level approximately 2°C. higher than that observed under minimal contact pressure. Thus, although it was possible to obtain a constant temperature reading with this system, the required contact pressure exceeded not only the capillary pressure but also the diastolic and the normal systolic blood pressure as well. Under these conditions total constriction of the skin capillaries directly under the thermojunction and con-

gestion of the surrounding blood vessels must occur. Ischemia of the skin per se would result in a lowering of the temperature, but since the skin is compressed between the thermocouple and the deeper tissues of higher temperature, the net result is a temperature reading considerably higher than readings at minimal pressure. Therefore, it may be assumed that the temperature observed under these conditions represents the temperature at some depth beneath the compressed skin. However, since the temperature attained was constant, this contact pressure was used in comparing the thermocouple reading of skin temperature rise under infrared irradiation with similar measurements made with the radiometer.

EFFECT OF INFRARED IRRADIATION

About half of the total solar energy at the earth's surface and practically all of the radiation impinging upon man from objects in his environment lie

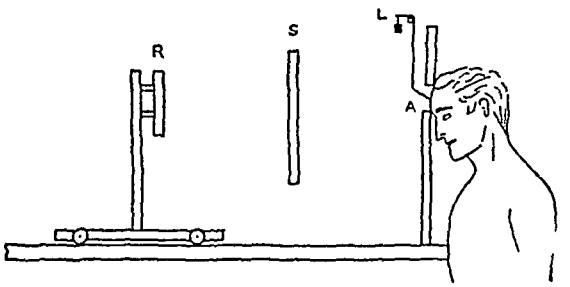

Fig. 5. APPARATUS FOR INFRARED IRRADIATION. R = radiation source. S = shutter. L = weighted lever. A = aperture through shield.

within the wavelength range of one to 20 μ of the infrared. Since this radiation is the main medium of exchange of heat between the body and its surroundings it is of prime importance physiologically. The non-penetrating infrared is almost completely absorbed within 0.05 mm. of the skin surface (6), and is particularly effective in altering skin temperature. To determine the effect of this radiation on thermocouple readings, measurements of skin-temperature rise due to non-penetrating infrared radiation were made with the thermocouple and compared with those made radiometrically under similar conditions.

The forehead was used for this portion of the study. The apparatus is shown in figure 5. It consisted of a screen with an aperture through which the subject's forehead was exposed to the radiation of a hot plate on opening of a shutter. The intensity of radiation was increased by moving the hot plate closer to the subject. The radiation at any given distance was measured with a radiometer. The unloaded thermocouple frame was suspended above the subject's head so that the thermocouple just touched the forehead. Weights sufficient to produce a force of 20 gm. were then loaded on the lever. When the temperature became constant, the shutter was opened and radiation of known intensity fell upon the forehead. The thermocouple readings were noted at 15-second intervals for one minute. The shutter was then closed and readings

taken for an additional 2 minutes, which was usually sufficient to permit the temperature reading to return to its initial level.

The elevation of the temperature produced by radiation of various intensities for periods of 15, 30, 45 and 60 seconds were plotted (fig. 6, part 1) and compared with similar data obtained with the radiometer (7) (fig. 6, part 2, redrawn from the original). Figure 6 represents average values and does not indicate the spread of individual readings. The ranges of the thermocouple readings were quite wide and in some instances elevations obtained for one period of irradiation overlapped those obtained for a longer or shorter period. All temperature elevations as measured with the thermocouple appeared to be

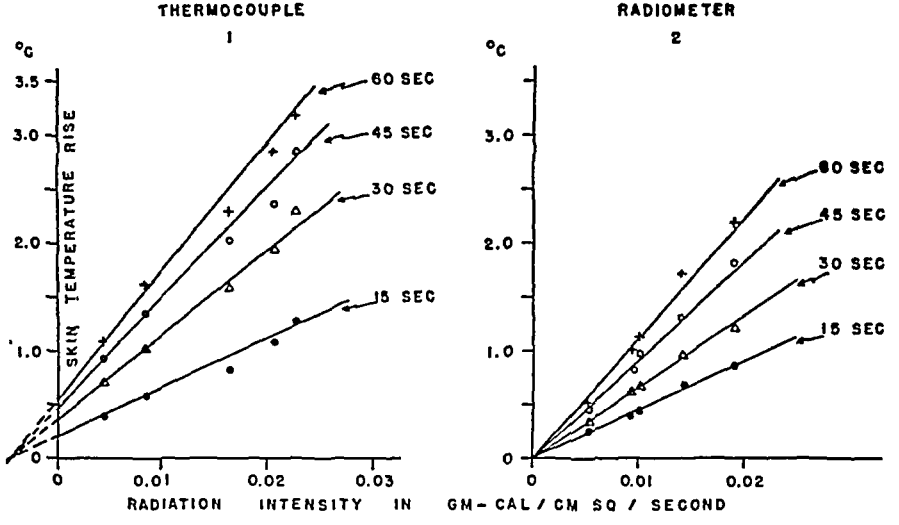

Fig. 6. TEMPERATURE RISE during infrared irradiation as measured with thermocouple vs. radiometer.

about one third greater than those measured with the radiometer. It will be noted that the thermocouple curves do not go through zero on extrapolation back to zero intensity, but that they do go through the same point on the base line. That this effect was due to the direct radiation to which the thermocouple was exposed on opening of the shutter was demonstrated by the following experiment. The thermocouple was suspended in air in the position it would occupy when in contact with the subject's head. The irradiation procedure was repeated and thermocouple readings noted at 15-second intervals as in the skin irradiation study. It was found that the thermocouple reading was markedly affected by the direct radiation on opening the shutter. At a radiation intensity of 10.4 m.c. per cm.^{2} per second, the thermocouple registered an immediate rise in temperature, which increased to a maximum of about 1°C. above the initial temperature after 45 seconds exposure. Since the percentage of the read-

ing due to this effect when the thermocouple is in contact with the skin cannot be calculated, it is impossible to correct for it and the value for temperature elevation at zero intensity represents the unavoidable error for this instrument in situations where thermal equilibrium does not exist. As shown in a previous study on an artificial surface, in thermal equilibrium the error during infrared irradiation is in the opposite direction (1).

Comment

The explanation for the reversal in the direction of the error in the thermocouple readings taken during temperature elevation from that of those taken during thermal equilibrium becomes clearer on consideration of the thermal conditions of the two situations. In both instances the thermocouple reading is a resultant of the combined effect of direct radiation from the stove and the temperature of the surface itself. In both instances the surface in contact with the thermocouple is shielded from the radiation by the thermocouple at the point of contact. However, at equilibrium the surface temperature remains constant and the difference in temperature between the surface and the source of radiation remains constant. The resultant temperature reading of the thermocouple is then slightly lower than the true surface temperature and this may be attributed to the shading effect of the thermocouple. Where the surface temperature is being raised by the radiation, the source is now at a relatively much higher temperature with reference to the surface than it is at equilibrium and the difference in temperature between the surface and the source is great initially, diminishing as the surface temperature rises. While the shading effect of the thermocouple is still present, the relatively greater radiation from the stove masks this effect and results in a temperature reading considerably higher than the true surface temperature. This effect is greatest on the initial exposure of the surface and the thermocouple to the radiation source and diminishes as the surface temperature approaches that of the radiation source.

In figure 6 it may be seen that the slopes of the curves for skin temperature rise as measured by the thermocouple agree fairly well with those as measured by the radiometer, indicating that the rate of change was followed faithfully although the amount of elevation as measured by the thermocouple was greater. Since the radiometer is exposed only to the surface and not to the radiation source it is unaffected by the direct radiation from the source to the skin. The difference in temperature elevation of the skin as measured by these two instruments may then be attributed to the exposure of the thermocouple to the direct radiation from the stove during irradiation of the skin.

MEASUREMENT OF THE AVERAGE TEMPERATURE OF THE BODY SURFACE

The instruments selected for investigation of the measurement of average skin temperature with thermocouples under ordinary laboratory conditions were: *1*) The no. 28 gauge copper-constantan thermocouple laid upon the skin and supported at either side of the junction with adhesive tape, leaving the thermojunction bare. *2*) The no. 28 gauge copper-constantan thermocouple applied to the skin by means of an adhesive tape strip covering the thermojunction. *3*) The no. 40 gauge copper-constantan thermocouple applied in the same manner as (*1*) above, leaving the thermojunction bare. *4*) The no. 40 gauge copper-constantan thermocouple glued to the skin with a thin layer of Duco cement over the thermojunction and about an inch of the leads.

The Dermal Radiometer was used for comparison readings. In making these measurements, the radiometer was held directly over the thermojunction in the case of the bare wire instruments, and as close as possible to one side of the site of the covered junctions.

The environmental conditions were normal room temperature (25°–30°C.), increased temperature sufficient to produce light sweating (34°–36°C.) and decreased temperature sufficient to cause slight shivering within about an hour (17.5°–19°C.).

Six sites on the exposed body surface were used, one thermocouple being applied to each area, the forehead, chest, abdomen, biceps, thigh and instep of the foot. In each experiment readings were taken of the temperature of each of the 6 sites, first with the thermocouples, then with the radiometer. About one minute was required for reading each series of 6 with either instrument. The 6 readings taken with each instrument were averaged and the average skin temperature obtained with each instrument was computed. The difference between the average skin temperature values (thermocouple value—radiometer value) was then found. Ten series of experiments were run under each of the experimental conditions. The 10 average skin temperature deviations were then averaged to obtain the average deviation under each experimental condition. Table 1 shows these average deviations and the range of the deviations for each instrument under each condition. For comparison analogous data obtained with these instruments on the leather surface have been included in the table. In the measurements made on the leather surface, 'normal' conditions were the same as those under which the average skin temperatures were measured. The 'hot' environment was simulated by irradiating the surface with infrared radiation from a hot-plate, and the 'cold' environment was produced by flowing air against the surface by means of an electric fan. All readings on the leather were made after the system had attained thermal equilibrium (*2*).

It will be seen from table 1 that in every instance save one, the error in

measurements taken on the skin is greater than that of those taken on the leather surface. The one exception is the no. 28 gauge bare wire readings in the hot environment. In this instance the error observed in measurements on the skin is smaller than those on the leather surface by more than 50 per cent. This is understandable since the rapid flow of blood in the dilated vessels of the warm skin tends to equalize the temperature on the exposed skin surface with that under the thermocouple wire. However, on the leather surface the thermocouple shades the area immediately underneath the wire from the radiation of the warm surfaces in the environment thus causing a low reading of

TABLE 1. AVERAGE DEVIATION IN DEGREES CENTIGRADE OF THERMOCOUPLE AND RADIOMETER MEASUREMENTS OF AVERAGE SKIN TEMPERATURE UNDER THREE DIFFERENT ENVIRONMENTAL CONDITIONS COMPARED WITH ANALOGOUS DATA OBTAINED ON A LEATHER SURFACE OF KNOWN TEMPERATURE (DEVIATION = THERMOCOUPLE VALUE − RADIOMETER VALUE)

THERMOCOUPLE	NORMAL ENVIRONMENT (25°C.–30°C.)				HOT ENVIRONMENT (34° C.–36°C.)				COLD ENVIRONMENT (17°C.–19°C.)			
	Skin		Leather Surface		Skin		Leather Surface		Skin		Leather Surface	
	Average Dev.	Range	Average Dev.	Range	Average Dev.	Range	Average Dev.	Range	Average Dev.	Range	Average Dev.	Range
	°C.	°C.	°C.	°C.	°C.	°C.	°C.	°C.	°C.	°C.	°C.	°C.
No. 28 gauge wire (adhesive tape)	0.7	−1.2 +1.6	0.18	−0.14 +0.41	0.5	−1.1 +0.3	0.18	−0.10 −0.29	0.8	−1.2 +1.5	0.08	−0.07 −0.14
No. 28 gauge wire (bare	0.4	−0.6 +0.5	0.20	−0.17 +0.84	0.2	−0.3 +0.6	0.49	−0.34 −0.60	0.4	−0.6 +0.7	0.27	−0.19 −0.33
No. 40 gauge wire (bare)	0.5	−0.2 +0.8	0.12	−0.22 +0.34	0.4	−0.7 +0.6	0.12	−0.24 +0.05	0.7	−2.1 +0.4	0.28	−0.17 −0.39
No. 40 gauge wire (glued)	0.3	−0.4 +0.4	0.22	−0.02 +0.40	0.2	0 +0.6	0.06	−0.07 +0.10	0.6	−1.0 +1.4	0.26	−0.22 −0.33

surface temperature. It is also seen that in the hot environment where the skin temperature most nearly approaches that of the environment, the average deviation for all instruments is somewhat less than it is in the other environments.

Comment

On the whole, average deviations and ranges of error are increased in the observations on the skin over those in the observations on the leather surface. These increases may be ascribed to the following two factors:

1) *Variability in temperature between areas measured by thermocouple and radiometer.* A. Pennes has reported a maximum difference in temperature of 0.73°C. between points on the skin within the radius of the radiometer field

(3). This was obtained by moving about on the skin, within the area observed by the radiometer, 4 Y-shaped thermocouples applied to the skin under the contact pressure produced by 0.58-gm. clamps attached to the tail and active wire of the thermocouple. This contact pressure was sufficient to produce a slight furrow in the skin. It has been shown by Remizov (5) that as little force as one gm. is sufficient to cause a skin temperature rise of 0.5°C. Although the contact pressure produced by Pennes' method of application was small, some local temperature effect was to be expected and would be greatest at the point of contact where the temperature was being measured. Furthermore, the normal fluctuations of the skin temperature might enhance or diminish this effect at any given moment. This method, therefore, could not yield precise data on the true temperature of the untouched skin, but does indicate the deviation which may be expected between readings made by the two methods.

B. Another factor contributing to the variability in temperature of adjacent areas is the rapidly changing temperature gradients in areas such as the hands and feet. In these areas the distal portions in the cold environment may be markedly cooler than more proximal areas and, therefore, a small difference in location of the temperature measurement site might yield a large difference between readings by the two methods.

2) *Variability of contact pressure. A.* In these experiments an attempt was made to maintain good thermal contact with a minimum of pressure on the skin in each type of application. Occasional large errors indicated that this attempt was not always successful. The bare wire thermocouples, and particularly the no. 40 gauge wire, exhibited a tendency to slip away from the adhesive tape supports. Frequent adjustment was required to maintain good contact. In the cold environment the tendency for the no. 40 gauge wire to slip was increased and these delicate wires were often broken in the attempt to draw them taut.

B. It was difficult to be certain that the junctions which were covered with adhesive tape were actually in contact with the skin. The spread of the range of error both above and below the previously observed figures with the same thermocouples uncovered indicated that this contact was not always optimal. However, interference with local sweating and protection of the skin from the environment may also contribute to this effect.

C. When the thermocouple was glued to the skin good contact was assured although the effects due to interference with sweating, protection from the environment and possible irritation of the skin by the glue could not be avoided.

The no. 28 gauge wire thermocouple gave the best performance on the skin although the no. 40 gauge bare wire thermocouples gave the best performance on the artificial surface. This can be accounted for by failure to obtain good thermal contact in application of the no. 40 gauge bare wire ther-

mocouple to the skin. This was particularly noticeable in the cold where the difference between the skin temperature and the environmental temperature was greatest; the average deviation was 0.7°C. with values ranging from −2.1°C. to +0.4°C. in this environment. Covering the junction with Duco cement improved the contact but in the cold this procedure introduced errors due to protection from the environment as shown by an increase of 1°C. in the upper limit of error while the lower limit of error was reduced by the same amount.

The no. 28 gauge bare wire thermocouple was sturdier, more easily handled and had less tendency to slip from the adhesive tape strips than the no. 40 gauge bare wire thermocouple. Under the conditions of these tests all average skin temperature values obtained with this instrument fell within ±0.7°C. of the radiometric value with average deviations no greater than 0.4°C. The same thermojunctions when covered with adhesive tape apparently were protected from the environment and interfered with sweating and heat loss so that the average deviations were twice as great as those observed previously with the thermojunctions bare.

The difficulty of securing good thermal contact with the no. 28 gauge wires and the fragility of the no. 40 gauge wires were distinct disadvantages which limit the practicality of their use. Furthermore, in using these instruments it is necessary that the environmental temperature remain fairly stable during the test period, that no direct drafts or direct radiation fall upon the test areas, and that the subject remain quiet since movement alters the contact of the bare junctions and may cause breakage of the delicate no. 40 gauge wires.

SUMMARY

The precision of thermocouples as skin thermometers has been studied by comparing the thermocouple readings of skin temperature with radiometer readings made under identical circumstances. The pressure of the thermocouple wire against the skin, the environmental conditions, and method of attachment of the thermocouple wires to the skin were altered to observe the influence of these factors on the performance of the thermocouple.

Pressure of the thermocouple against the skin, sufficient to produce a stable temperature reading, increased skin temperature by as much as 2°C. Therefore, it was concluded that methods of application requiring appreciable pressure are unsuitable for the measurement of true skin temperature. During infrared irradiation of the skin large errors were introduced into the thermocouple reading of skin temperature by the heating of the thermocouple itself. It was concluded, therefore, that this instrument is unsuitable for the accurate measurement of skin temperature during irradiation of the site. Comparisons of radiometric and thermocouple measurements of average skin temperature

under normal, hot and cold environmental conditions indicated that *a*) the no. 28 gauge bare junction thermocouple gave values within ±0.6°C. of the radiometer readings under all conditions; *b*) the no. 28 gauge thermocouple applied to the skin with adhesive tape covering the junction yielded deviations which were twice as great as those of the bare wire thermocouple readings; and *c*) the no. 40 gauge bare junction thermocouple was unsatisfactory because of its fragility and the difficulty of obtaining good thermal contact.

It was concluded that of these instruments the no. 28 gauge bare wire thermocouple may be used successfully for determination of average skin temperature of the quiet subject under limited environmental conditions where an average accuracy of ±0.4°C. is sufficient.

The authors gratefully acknowledge the technical assistance of Mr. J. M. Manring.

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Arterial Blood pH and pCO_2 Changes in Response to CO_2 Inhalation after 24 Hours of Passive Hyperventilation[1]

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IN A RECENT COMMUNICATION (1) it was shown that in the normal human subject there is an increased respiratory response to CO_2 following prolonged passive hyperventilation at normal oxygen tension. In the experiments reported, data were not available to ascertain the relationships between the plasma pCO_2 and (H^+) and the respiratory drive. Since the occurrence of increased sensitivity to CO_2 after prolonged hyperventilation has an important bearing on the theoretical analysis of the respiratory control mechanism, it seemed important to study the plasma pCO_2 and (H^+) in relation to respiratory minute volume in subjects breathing various CO_2 mixtures before and after prolonged passive hyperventilation. In particular we wished to ascertain whether, and to what degree, the respiratory minute volumes at given plasma pCO_2 and (H^+) were changed after such hyperventilation.

In order to study this problem, respiratory minute volume changes and arterial blood pH and bicarbonate changes in response to inhalation of three different CO_2/O_2 mixtures before and after 24 hours of passively imposed hyperventilation were measured on 2 healthy young men.[2]

EXPERIMENTAL PROCEDURE

The methods of producing the hyperventilation and of determining respiratory minute volume, arterial plasma pH and plasma CO_2 content have been described previously (1). Arterial blood samples were drawn when the subject had reached a steady state, as indicated by respiratory minute volume determinations while breathing 100 per cent oxygen, 3 per cent CO_2 in oxygen, 5 per cent CO_2 in oxygen, and 7 per cent CO_2 in oxygen in that order. These blood samples were obtained by means of an indwelling needle in the radial artery using the technique described by Wood (2). Sodium heparin powder was used as the anticoagulant. Carbon dioxide tensions were calculated from pH

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[1] Aided by a grant from the National Foundation for Infantile Paralysis, Inc.
[2] The respirator employed was the commercial model of the J. H. Emerson Company, to whom we are indebted for its loan.

and CO_2 content by means of the Henderson-Hasselbalch equation using the value 6.11 for pK′.

RESULTS AND DISCUSSION

Respiratory minute volumes, arterial plasma CO_2 content, pH, and pCO_2 with the subject at steady state on each of the gas mixtures before and after

TABLE 1. VENTILATION RESPONSE, PLASMA pH, CO_2 CONTENT AND CO_2 TENSION WITH SUBJECTS AT STEADY STATE BREATHING OXYGEN-CO_2 MIXTURES

MIXTURE BREATHED	RESP. MIN. VOLUME	PLASMA CO_2 CONTENT	PLASMA pH[1]	PLASMA $(H^+) \times 10^9$	ARTERIAL BLOOD pCO_2
%	*l.*	*vol. %*			
		Subject J. R.			
		Before Hyperventilation			
100 O_2	8.1	55.9	7.32	47.8	47.4
3 CO_2	14.4	56.6	7.28	52.8	52.4
5 CO_2	26.0	60.7	7.22	60.3	63.6
7 CO_2	39.3	63.2	7.14	72.4	78.6
		After Hyperventilation			
100 O_2	12.6	41.0	7.38	41.7	30.4
3 CO_2	17.2	47.2	7.32	47.8	40.4
5 CO_2	37.6	49.8	7.28	52.5	45.9
7 CO_2	58.5	55.8	7.14	72.4	69.4
		Subject R. N.			
		Before Hyperventilation			
100 O_2	10.1	60.5	7.32	47.5	50.8
3 CO_2	17.1	61.8	7.29	51.7	56.2
5 CO_2	37.9	63.2	7.26	54.5	60.4
7 CO_2	64.7	67.5	7.23	58.9	71.9
		After Hyperventilation			
100 O_2	12.8	50.8	7.31	49.6	44.4
3 CO_2	23.6	52.5	7.30	50.5	46.7
5 CO_2	60.2	55.1	7.27	54.3	52.5
7 CO_2	92.3	59.1	7.19	64.4	65.9

[1] The pH values appear to be low for arterial plasma of normal subjects, and the calculated carbon dioxide tension therefore correspondingly high. However, since all of the blood pH determinations were made on the same instrument and against the same buffer solution as a standard, it is felt that the relative values are valid although the absolute values may be low due to an incorrect value on the standard buffer solution.

24 hours of hyperventilation are presented in table 1. Again it is apparent that after passive hyperventilation of this duration, inhalation of a given CO_2 mixture produced a greater respiratory response than before hyperventilation. With the additional data of arterial blood pH and pCO_2, this change in response can be related to each of these variables in the arterial blood. Figure 1 presents the 4 graphs showing these relationships. Hydrogen ion concentrations were calculated from pH and are expressed as moles per liter times 10^9. Straight lines have been fitted to the points by the method of least squares, and the

lines have been extrapolated to the abscissa in order to determine the apnea point, i. e. the pCO_2 or the (H^+) at which no stimulus for respiration would be present. The point for 7 per cent CO_2 after hyperventilation with *subject R. N.* was omitted from the calculation of the slope and position of the curves because it was found that this was a maximum response for this subject. An increase in the slope of the response curve when minute volume is plotted against pCO_2 is apparent in each of the subjects. It can also be seen that the curves have been displaced to the left and the apnea point lowered. This would indicate that a given absolute arterial blood pCO_2 is associated with a larger respiratory minute volume and also that a given increment in pCO_2 is producing a greater increment in minute volume. In the plot of arterial blood

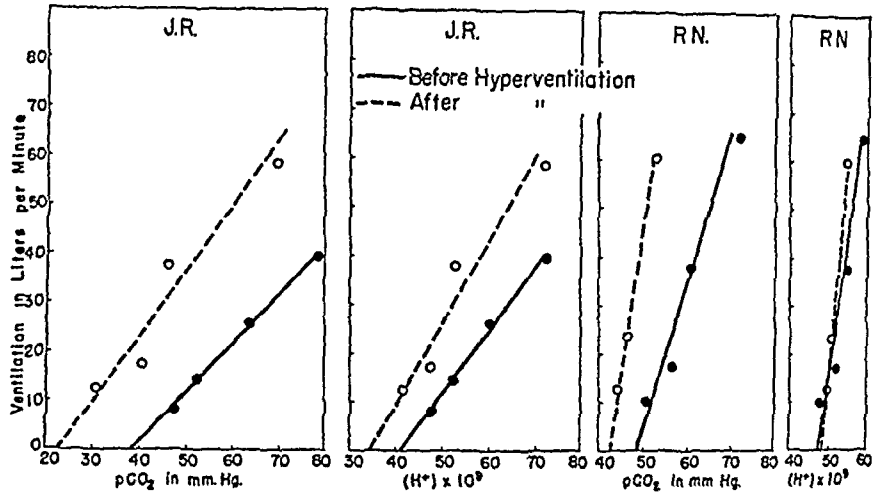

Fig. 1. RESPIRATORY RESPONSE to increased arterial blood pCO_2 and (H^+) produced by breathing CO_2 enriched gas mixtures before and after 24 hours of passive hyperventilation in 2 human subjects.

(H^+) against respiratory minute volume, the slope is increased and the curve shifted to the left for *subject J. R.* while both the slope and the position are essentially unchanged for *subject R. N.*

The data as obtained in the present experiment make it possible to construct *in vivo* CO_2 absorption curves of plasma (fig. 2) for the 2 subjects. In both instances a reduction in alkali reserve after 24 hours of passively imposed hyperventilation can be seen. With the reduction in bicarbonate concentration that accompanies prolonged respiratory alkalosis, a given pCO_2 would produce a greater (H^+). This explanation has been utilized to account for the continued overbreathing that follows prolonged hypoxic hyperventilation when normal oxygen tension is restored (3, 4). Bjurstedt (5) states that whereas the original stimulus for increased respiration in hypoxic hyperventilation is the low oxygen tension (essentially reflexogenic), after the alkali reserve has been lowered and compensation has taken place, the drive for continued overbreathing is the need for removal of CO_2 (primarily centrogenic).

If arterial blood concentrations alone are considered, however, this need for removal of CO_2 cannot be invoked as the sole explanation for the increased response to CO_2 in the present experiments, since after hyperventilation a greater respiratory response was produced by a lower pCO_2 and a lower (H^+) than before hyperventilation. For example, in the case of J. R., before hyperventilation an arterial blood pCO_2 of 47.4 and a pH of 7.32 were producing a respiratory response of 8.1 liters per minute whereas after hyperventilation a pCO_2 of 30.4 and a pH of 7.38 gave a response of 12.6 liters per minute. Similar differences can be seen throughout the series.

These data confirm Gray's findings (6) that an increase in the responsiveness of the respiratory center to CO_2, which is not entirely attributable to

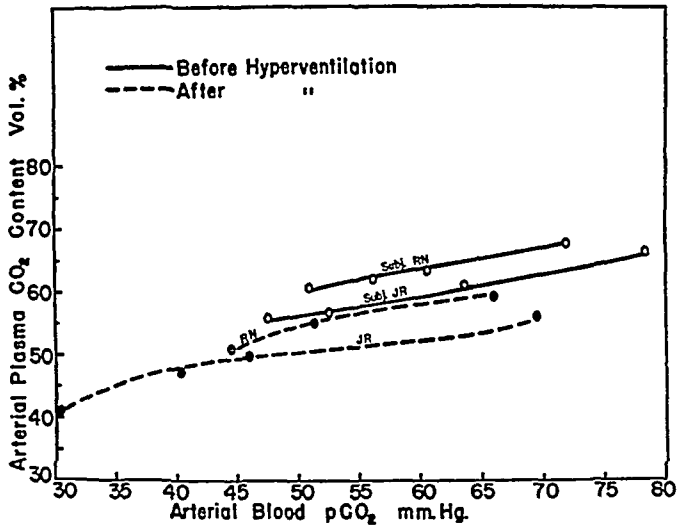

Fig. 2. IN VIVO PLASMA CO_2 absorption curves for 2 subjects before and after 24 hours of hyperventilation.

the fall in blood alkali reserve, follows prolonged hyperventilation. The possibility that this increased responsiveness may be due to a decrease in the intracellular buffer content of the respiratory center cells is investigated in the following paper(7).

SUMMARY AND CONCLUSIONS

Respiratory responses to oxygen and to 3 different concentrations of CO_2 in oxygen before and after 24 hours of passively imposed hyperventilation were obtained on 2 normal adult subjects. When the subjects had reached a steady state breathing each of the gas mixtures, an arterial blood sample was obtained for pH and CO_2 content determinations. Using these data arterial blood pCO_2 was calculated for each of the blood samples. When respiratory minute volume is plotted against arterial blood pCO_2 an increase in the slope of the line and a

displacement to the left after hyperventilation is apparent for both of the subjects. The graph of minute volume as a function of arterial blood (H^+) shows a similar displacement and change in slope for *subject J. R.* but for *subject R. N.* the slope and position are essentially unchanged. The increase in response to CO_2 which has been shown to exist after 24 hours of passively imposed hyperventilation cannot be explained in these experiments entirely on the basis of the reduced bicarbonate concentration of the blood which takes place with prolonged overbreathing.

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Changes in Brain pH Response to CO_2 after Prolonged Hypoxic Hyperventilation

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PERSISTENT HYPERVENTILATION following prolonged overbreathing of hypoxic origin (1) and of mechanically induced origin (2) has been reported. The fall in alkali reserve of the blood during the time of the hyperventilation has been suggested as the mechanism for this continuing hyperventilation after the initial cause has been removed (3). In experiments in which the arterial blood pH and CO_2 content of the subject were determined at the same time that the respiratory minute volume response was recorded, it was found that reduction in alkali reserve of the blood would not account entirely for the increased respiratory responsiveness to CO_2 inhalation following 24 hours of passive hyperventilation (4).

It has been suggested that the respiratory center becomes more sensitive to CO_2 after prolonged acapnia (5) but no mechanism to explain such an increase in sensitivity has been proposed.

The present study was undertaken following the suggestion that a reduction in buffer capacity for CO_2 of the cells of the respiratory center themselves might play a part in this mechanism. On the assumption that the respiratory center cells would reflect changes in the brain as a whole, a method was devised for determining the CO_2 titration curve of brain homogenate.

Such titrations have been carried out on the brains of 10 pairs of guinea pigs, one animal of each pair having been exposed to hypoxic hyperventilation for 24 hours and the other animal of each pair having been kept under similar laboratory conditions but at normal oxygen tension.

METHODS

Hypoxic hyperventilation was produced by placing the guinea pigs in a metal chamber 6′ in length and 2.5′ in diameter and evacuating the chamber to a pressure of approximately 290 mm. Hg pressure. This low pressure was maintained with a continuous ventilation through the chamber for the 24-hour period. During this time both the experimental and the control animals were given water but no food. Immediately upon removing the guinea pig from the

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chamber it was decapitated along with its control mate and the heads were immediately frozen in liquid air.

The solidly frozen brain was then removed and ground to a fine powder in a cold mortar. Two grams of this powdered brain were weighed to the nearest 5 mg., and 20 ml. of cold distilled water were added. The brain and water mixture was kept frozen to a mushy ice and ground to a smooth homogenate in a mortar. Five-ml. aliquots of this homogenate were placed in 500-ml. tonometers and one of three CO_2/O_2 mixtures flushed through the tonometer. The CO_2 mixtures contained 1.80 per cent, 3.17 per cent, and 4.99 per cent CO_2 in oxygen. Gas analyses were made with the .5-ml. Scholander analyzer (6). Equilibration of the homogenate with the gas mixture was carried out by ro-

TABLE 1. HYDROGEN ION CONCENTRATIONS, EXPRESSED AS M/L × 10^8 OF BRAIN HOMOGENATES EXPOSED TO DIFFERENT CO_2 TENSIONS FOR NORMAL AND HYPOXIC HYPERVENTILATED GUINEA PIGS

GUINEA PIG PAIR NO.	1.80% CO_2		3.17% CO_2		4.99% CO_2	
	Normal	Hyperventilated	Normal	Hyperventilated	Normal	Hyperventilated
1	26.9	33.1	42.7	47.9	56.2	66.1
2	28.1	33.1	42.7	51.3	58.9	70.8
3	26.3	25.7	44.7	39.8	66.1	55.0
4	27.5	26.9	34.7	49.0	56.2	66.1
5	27.5	25.7	42.7	41.7	58.9	66.1
6	28.8	32.4	39.8	44.7	64.6	58.9
7	29.5	33.9	42.7	51.3	57.5	64.6
8	30.2	34.7	44.7	53.7	64.6	75.9
9	25.1	35.5	38.9	55.0	57.5	70.8
10	28.8	28.8	44.7	42.7	63.1	64.6
Ave.	27.87 ± 0.51	30.98 ± 1.26	41.83 ± 1.06	47.71 ± 1.75	60.36 ± 1.26	65.89 ± 1.96

tating the tonometer on an ice bath for 15 minutes. At the end of this time the homogenate was taken up without exposure to air into 5-cc. syringes and the pH of each sample was determined with a glass electrode pH meter maintained at 17°C. in a constant temperature room. Approximately 5 minutes were allowed for the homogenate to come up to the temperature of the glass electrode after removal from the ice bath and before the pH was determined. The glass electrode was checked against a standard buffer before and after each determination and duplicate determinations were made on each sample. Reproducibility of the pH value by this method was usually within .005 pH units. The entire procedure from decapitation to pH determination was carried out on one pair of guinea pigs in the same afternoon.

The average barometric pressure on the days of the experiment was 741 mm. Hg and this figure was used in computing the pCO_2 for the various mixtures.

RESULTS

The hydrogen ion concentrations as calculated from the pH's of the brain homogenate at the different CO_2 tensions are presented in table 1. The mean (H^+) at all CO_2 tensions was greater for the animals that had been exposed to 24 hours of hypoxic hyperventilation than it was for the controls. As might be expected, there is a greater variation among the animals of the hyperventilated group than there is among the control group. However, an examination of the data by the method of analysis of variance indicates that there is a probability of less than 0.01 that the differences between the hypoxic hyperventilated animals and the control animals could have occurred by chance alone.

When comparisons between control and hyperventilated animals are made by animal pairs, it can be seen that in 7 cases the change is in the direction of a given pCO_2 producing a lower pH, in 2 cases (*pairs 5* and *10*) there is very little difference between the members of the pair, and in one pair (*no. 3*) the change is in the opposite direction.

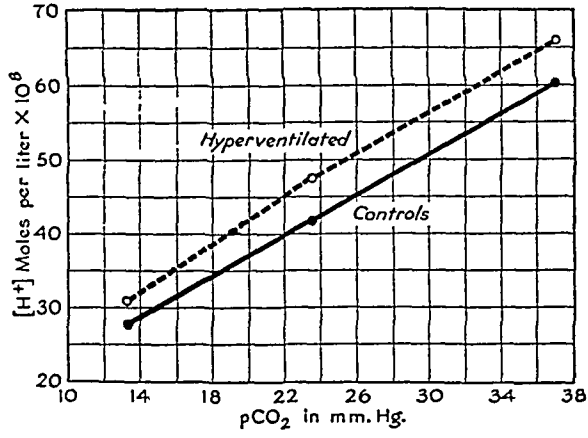

Fig. 1. Effect of 24 hours of hypoxic hyperventilation on the CO_2 titration curves of guinea pig brain homogenate.

The curves of the average hydrogen ion concentration as a function of pCO_2 for the 2 groups are presented in figure 1. The difference in position of the two groups is apparent but any difference in slope of the 2 curves is not significant.

DISCUSSION

In previous work (7) the acid-base changes resulting from prolonged mechanically induced hyperventilation in the presence of normal oxygen tension have been found to be essentially the same as those resulting from hypoxic hyperventilation. For convenience in these experiments hypoxia was utilized as the means of producing hypocapnia.

It is recognized that the method of determining the CO_2 titration curve

of the brain included the extracellular as well as the intracellular components, and a reduction in the buffer content of the extracellular components would influence the position of the curves for the brain as a whole. However to account for the differences on this basis alone would require a fall in plasma alkali reserve several times as large as those which have been observed in humans subjected to 24 hours of hyperventilation.

Although CO_2 exerts a stimulating effect on the respiratory center apart from its effect on pH, it must also be considered in the effect it has on the hydrogen ion concentration. It is conceivable that the stimulating effect of a given pCO_2 in the arterial blood would be enhanced if that CO_2 tension produced a lower pH in the respiratory center cells. Such a reduction in buffer content of these cells might account for the increased sensitivity of the center to CO_2 following prolonged hyperventilation. In this connection it should be pointed out that a marked fall in the plasma level of inorganic phosphate has been found to take place with hyperventilation (7, 8). A shift of this anion from extracellular compartment into the chemosensitive cells of the respiratory center might be concerned in this mechanism.

SUMMARY AND CONCLUSIONS

The CO_2 titration curves of brain homogenate were determined for 10 guinea pigs which had been exposed to hypoxic hyperventilation for 24 hours and for 10 normal guinea pigs. A given pCO_2 produced a lower pH in the brain homogenate of the hyperventilated animals than it did in the controls. It is suggested that this reduction in the buffering ability of the brain for CO_2 following prolonged hyperventilation may be the mechanism by which the increased sensitivity of the respiratory center to CO_2 following such prolonged hypocapnia is brought about.

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Occurence in Normal Individuals of Diurnal Variations in Olfactory Acuity[1]

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IN RECENT REPORTS (1, 2) from this laboratory experiments were described suggesting the existence in normal individuals of diurnal variations in olfactory acuity. The pattern of these variations was claimed to be remarkably uniform and intimately connected with ingestion of food. Meals were stated to be preceded by a period of increasing and followed by one of decreasing acuity of olfaction. The decrease in olfactory acuity appeared to depend upon ingestion of food because it failed to occur when meals had been omitted. These observations led to the tentative conclusion that precibal increase and postcibal decrease in olfactory acuity may represent measurable changes characteristic of and concomitant with a conversion of the sensation of appetite into one of satiety.

Sufficient information has been obtained from studies conducted in this laboratory during the past three years so that evidence may be presented in support of the original assertion regarding the existence in normal individuals of diurnal variations in olfactory acuity. The present communication was prepared with this purpose in mind.

METHODS

Olfactory thresholds were determined by means of a method originally described by Elsberg and Levy (3). In principle it consists of injecting variable but measurable volumes of odorous air into both nasal passages of an individual during a period of momentary cessation of breathing, the force of the injection taking the place of ordinary inspiratory movements. As the volume injected and its pressure are known, the test is a quantitative one.

The apparatus used for the test includes a bottle of 530-cc. volume containing a constant amount of odorous substance. The bottle is closed by a rubber stopper which contains inlet and outlet tubes. A nosepiece ending in

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[1]This paper reports research undertaken in cooperation with the Quartermaster Food and Container Institute for the Armed Forces, and has been assigned number 286 in the series of papers approved for publication. The views or conclusions contained in this report are those of the authors. They are not to be construed as necessarily reflecting the views or the indorsement of the Department of the Army.

two olives is connected with the outlet tube by means of a pure gum rubber tube which is compressed by a pinch-cock. The inlet tube is connected with a syringe permitting injection into the bottle of variable but measurable volumes of air. Care is taken to assure air-tightness throughout the system.

The procedure consisted of injecting a known volume of air into a bottle and of releasing it into the nasal passages of the subject by pressing upon the pinch-cock. The smallest volume of odorous air which sufficed to produce the sensation of the odor used was interpreted as the measure of threshold for the sense of smell for the subject at the time. At each determination, the threshold value accepted for the subject was the smallest volume of odorous air which produced the sensation of the particular odor three times in succession.

The odor used in the experiments here reviewed was that of coffee. Ground coffee of a standard brand and in constant amounts (22 gm.) was renewed in the bottle regularly once a month.

On test days the subjects were examined regarding patency of their nasal passages. This was done by having them exhale through their nose upon a metal mirror. On the polished surface of the mirror the spots produced by the vapor from each side of the nose had to be of equal size and fade out at an equal rate. Only when these requirements were fulfilled could the subject participate in the study.

The procedure was fully explained to the subjects. They were instructed to insert the nosepiece and to hold it in place so as to permit the escaping odorous air to reach the olfactory region of the nose. They were requested to state whether or not they could recognize the odor upon its escape into the nose during the moment of cessation of breathing. Sensations which were perceived at a later moment were disregarded. The subjects had to remove the nosepiece and breath restfully for 30 to 60 seconds between successive trials.

The threshold determinations were performed between 9:30 and 10:00 A. M. and between 11:30 A. M. and 12 noon and between 1:00 and 1:30 P. M. and between 4:00 and 4:30 P. M. On test days the subjects' statements regarding hunger and appetite were recorded as well as their freely selected caloric intake at breakfast, lunch and dinner time. On these days the subjects had been requested to abstain from taking food between meals.

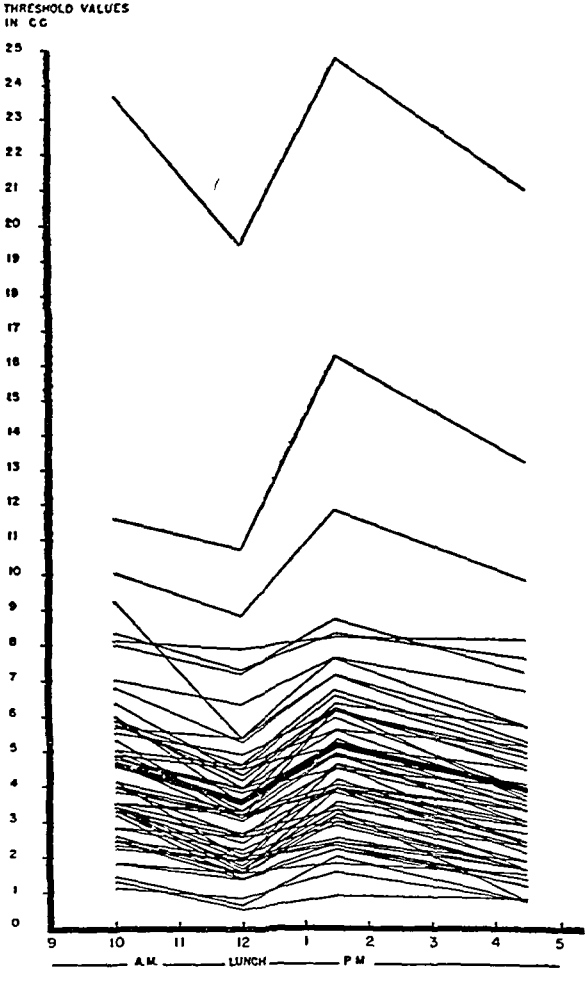
There were 58 individuals, 50 females and 8 males, who served as subjects. They were in apparently good health, ranging in age from 17 to 49 years. They held clerical and technical positions in this institution and worked daily from 9 A. M. until 5 P. M. As a rule they had breakfast and dinner at home at customary hours, but ate lunch in the hospital cafeteria which offered a variety of dishes, permitting reasonably free selection of food. Lunch was served between 12 noon and 1 P. M.

The results presently to be discussed are those of olfactory threshold determinations performed in all subjects on days on which the subjects observed normal food habits. Also to be analyzed are the results of olfactory threshold

determinations performed in some of the subjects on days on which the subjects omitted their noon meal.

ANALYSIS OF RESULTS AND OBSERVATIONS

Days on Which Subjects Observed Normal Food Habits. Available for analysis are the results of tests performed in the 58 subjects on 1521 test days. The number of test days for the subjects ranged from 9 to 140, with a group average of 26 days. Figure 1 shows averages of olfactory threshold values obtained at different hours of test days. The illustration demonstrates a decrease of olfactory threshold values during the morning hours, an increase following ingestion of lunch and another decrease of olfactory threshold values during the later afternoon. Variations in olfactory threshold values of the pattern described were obtained on 1005 (66.1%) of the 1521 days. The increase of olfactory threshold values failed to be demonstrable on but 203 (13.4%) of the test days. On 171 (11.2%) test days no decrease of olfactory threshold values was noted during the morning hours. On 111 (7.3%) test days the threshold determinations failed to reveal a decrease in olfactory threshold values during the later afternoon. On 31 (2%) test days an increase was noted of olfactory threshold values following ingestion of lunch but a decrease of threshold values was noted neither during the morning nor during the later afternoon.



Olfactory threshold values obtained at different hours of test days and expressed in terms of averages

LIGHT LINES FOR THE INDIVIDUALS. HEAVY LINE FOR THE GROUP

Fig. 1

The nature of the study at hand, however, requires a detailed analysis not of the results obtained for the group but rather of those obtained for individual subjects. Therefore, an inquiry was made as to whether or not the averages of olfactory threshold values obtained for the subject at different hours differed significantly from each other. The results of these calculations are shown in table 1. The values in columns *A*, *B* and *C* indicate the average differences expressed as cc. of odorous air between threshold values obtained at 10:00 and 12 o'clock A. M. (*A*); between threshold values obtained at 12 noon and 1:30 P. M. (*B*); and between threshold values obtained at 1:30 and 4:30 P. M. (*C*). The values in column *P* indicate the respective probability (calculated by means of Student's *t* value (4)) that these differences are not significantly greater than zero. Statistical convention justifies the assumption that probability values of 0.05 or less are indicative of significance. This is to say that differences between the averages of threshold values are significant if the probability that they are not significant is 0.05 or less.

In all subjects the olfactory threshold values in average decreased during the morning, increased following ingestion of lunch and decreased during the later afternoon. The three average differences are found to be significant in 54 of the 58 subjects. In 2, *subjects 55* and *56*, of the remaining 4 subjects the average decrease of threshold values during the later afternoon is insignificant. In one, *subject 57*, of the 4 subjects the decrease during the morning is insignificant. There is noted, however, in these 3 subjects a significant increase in average olfactory threshold values following ingestion of lunch. In but one of the 58 subjects, *subject 58*, all 3 differences fail to be of significant magnitude.

Days on Which the Subjects Omitted Their Noon Meal. In this series of experiments 8 of the subjects cooperated. Threshold determinations were performed in the manner described. Days on which the subjects omitted their noon meal were preceded and followed by days on which they observed normal food habits. There were 44 test days for the group on which lunch had been omitted and 490 test days on which normal food habits had been observed. For individual subjects the number of these test days ranged from 4 to 9 and from 30 to 140, respectively. Figure 2 shows averages of olfactory values obtained at different hours of both kinds of test days. As can be seen from the illustration there was no increase of olfactory threshold values noted on days on which lunch had been omitted. This observation held true for all 44 test days.

To establish reliability and significance of this observation, it appeared desirable to subject to statistical analysis the results obtained for individual subjects. For this purpose an inquiry was made as to whether or not the differences between averages of olfactory threshold values obtained immediately before and shortly after lunch time on days on which lunch had been ingested differed significantly from the differences between like averages of olfactory threshold values obtained on days on which lunch had been omitted. The re-

TABLE I. AVERAGE DIFFERENCES BETWEEN OLFACTORY THRESHOLD VALUES OBTAINED AT DIFFERENT HOURS OF TEST DAYS (expressed as cc. of odorous air).

SUBJECT	NO. OF TEST DAYS	DIFFERENCE A (DECREASE)	P_A	DIFFERENCE B (INCREASE)	P_B	DIFFERENCE C (DECREASE)	P_C
1	9	−2.2	<0.005	+3.1	<0.005	−2.5	<0.005
2	9	−1.8	<0.005	+1.6	<0.005	−1.3	0.02
3	10	−1.3	<0.005	+2.0	<0.005	−1.1	0.01
4	10	−0.6	<0.005	+0.6	<0.005	−0.8	<0.005
5	11	−0.8	0.04	+1.1	<0.005	−1.5	<0.005
6	11	−0.9	<0.005	+1.3	<0.005	−1.2	<0.005
7	11	−0.5	0.01	+0.6	0.04	−1.0	<0.005
8	11	−0.3	<0.005	+0.5	<0.005	−0.5	0.02
9	11	−1.6	<0.005	+0.8	<0.005	−1.0	<0.005
10	11	−0.7	0.01	+1.5	<0.005	−1.7	0.01
11	11	−1.3	0.005	+3.0	<0.005	−2.4	<0.005
12	13	−0.8	<0.005	+0.8	0.01	−0.7	0.005
13	13	−0.7	0.02	+1.4	<0.005	−1.0	<0.005
14	14	−0.8	<0.005	+1.1	<0.005	−0.8	0.01
15	14	−1.8	<0.05	+3.0	<0.005	−2.4	<0.005
16	15	−0.3	0.04	+0.7	<0.005	−0.8	<0.005
17	16	−2.4	<0.005	+2.5	<0.005	−1.3	<0.005
18	16	−0.3	0.04	+0.8	<0.005	−0.6	<0.05
19	17	−1.4	<0.005	+1.8	<0.005	−1.9	<0.005
20	17	−0.8	0.007	+1.6	<0.005	−1.5	<0.005
21	17	−0.6	<0.005	+0.8	<0.005	−0.6	<0.005
22	17	−0.4	<0.005	+1.0	<0.005	−0.7	<0.05
23	18	−1.0	0.05	+5.2	<0.005	−3.2	<0.005
24	18	−2.0	<0.005	+1.5	<0.005	−2.1	<0.005
25	18	−1.8	<0.005	+2.0	<0.005	−1.9	<0.005
26	18	−1.0	<0.005	+1.1	<0.005	−0.7	0.02
27	19	−1.7	<0.005	+1.5	<0.005	−1.2	<0.005
28	19	−2.2	<0.005	+2.2	<0.005	−1.7	<0.005
29	19	−1.1	<0.005	+0.8	<0.005	−0.9	<0.005
30	19	−1.3	<0.005	+2.1	<0.005	−1.4	<0.005
31	20	−0.9	<0.005	+1.8	<0.005	−1.5	<0.005
32	21	−1.4	<0.005	+2.2	<0.005	−1.7	<0.005
33	22	−1.5	<0.005	+2.0	<0.005	−1.9	<0.005
34	22	−2.2	<0.005	+1.7	<0.005	−2.0	<0.005
35	22	−0.3	0.05	+1.6	0.05	−1.4	<0.005
36	23	−0.3	0.005	+0.6	0.005	−0.9	<0.005
37	24	−0.5	0.01	+0.7	<0.01	−0.5	<0.02
38	24	−0.8	<0.005	+1.0	<0.005	−0.9	<0.005
39	25	−0.3	<0.005	+0.3	<0.005	−0.2	<0.005
40	27	−0.8	<0.005	+1.5	<0.005	−1.4	<0.005
41	30	−0.9	<0.005	+1.5	<0.005	−1.3	<0.005
42	30	−1.4	<0.005	+2.0	<0.005	−1.6	<0.005
43	32	−0.6	<0.005	+0.5	<0.005	−0.6	<0.005
44	35	−1.5	<0.005	+1.8	<0.005	−1.4	<0.005
45	38	−0.7	<0.005	+1.2	<0.005	−1.0	<0.005
46	40	−1.3	<0.005	+1.4	<0.005	−1.3	<0.005
47	48	−1.4	<0.005	+0.8	<0.005	−1.2	<0.005
48	50	−1.9	<0.005	+2.4	<0.005	−2.6	<0.005
49	54	−4.3	<0.005	+5.2	<0.005	−3.8	<0.005
50	54	−0.7	<0.005	+0.8	<0.005	−0.7	<0.005
51	94	−0.9	<0.005	+1.3	<0.005	−1.1	<0.005
52	94	−0.7	<0.005	+1.1	<0.005	−0.9	<0.005
53	98	−1.0	<0.005	+1.2	<0.005	−1.1	<0.005
54	140	−0.6	<0.005	+0.9	<0.005	−0.7	<0.005
55	15	−0.4	0.04	+1.0	0.04	−0.3	<0.005
56	9	−0.5	<0.005	+0.6	<0.005	−0.5	0.07
57	15	−0.4	0.065	+0.7	0.065	−0.5	0.03
58	19	−0.4	0.15	+0.5	0.15	−0.4	0.15

A = Average difference between threshold values obtained at 10:00 A.M. and noon. B = noon and 1:30 P.M. C = 1:30 and 4:30 P.M. P = Probability that the respective difference is not significantly greater than zero.

sults of these calculations are shown in table 2. The values in columns B_1 and B_2 represent the average differences expressed as cc. of odorous air between threshold values obtained at 12 noon and 1:30 P. M. on days on which lunch had been ingested (B_1) and on days on which lunch had been omitted (B_2). The values in column P indicate the probability (calculated by means of Student's t value) that the difference between the differences referred to is not significant. Applying statistical convention, values of 0.05 or less are to be

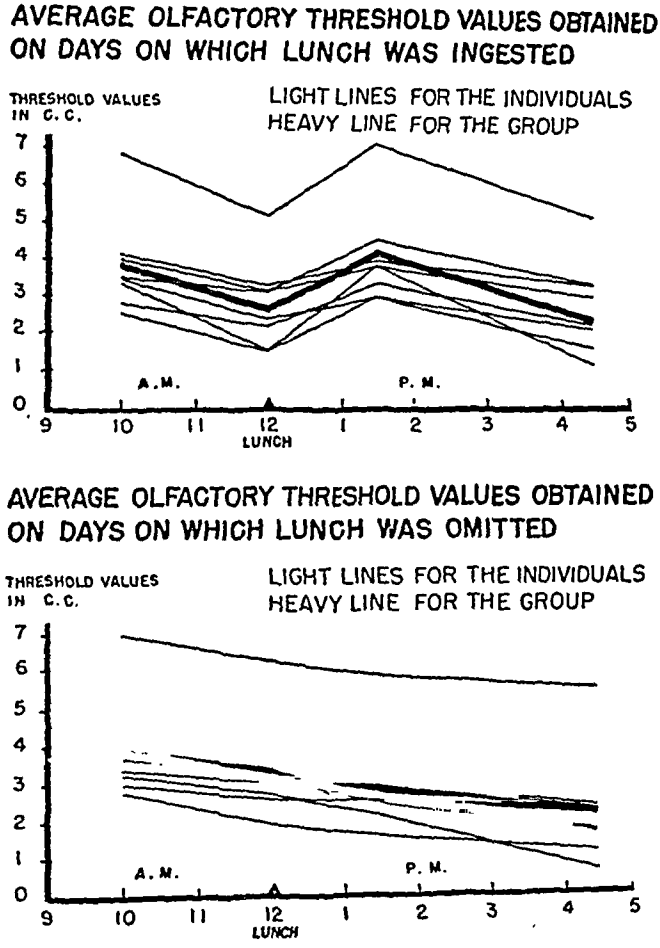


Fig. 2

considered indicative of significance. Again, this means that a difference is significant if the probability that it is not significant is 0.05 or less. From the table it can be seen that the difference under discussion is significant for all subjects.

COMMENT

Changes in olfactory threshold values indicate changes in acuity of olfaction. Thus, decreasing threshold values signify an increase, increasing threshold values a decrease in acuity. Therefore, the information presented reveals that

the olfactory acuity was found to be greater before than shortly after ingestion of noon meals on 1005 (86.7%) of the 1521 test days; an increase in olfactory acuity during the morning was noted on 1350 (88.8%) and an increase during the later afternoon on 1410 (92.7%) of the test days. Considering the multitude of variables inherent in a procedure as the one employed in the present investigation, the high percentages cited appear to indicate reliability of the observations. Additional confirmation of this impression may be deduced from the analysis of results obtained for individual subjects. This analysis taking into account averages of olfactory threshold values obtained for the individual subjects at different hours of test days reveals that there were demonstrable in 54 of the 58 subjects a statistically significant increase in olfactory acuity before lunch, a statistically significant decrease shortly after ingestion of the

TABLE 2. AVERAGE DIFFERENCES BETWEEN OLFACTORY THRESHOLD VALUES OBTAINED BEFORE AND AFTER LUNCH TIME (expressed as cc of odorous air)

SUBJECT	NO. OF TEST DAYS ON WHICH LUNCH WAS INGESTED	NUMBER OF TEST DAYS ON WHICH LUNCH WAS OMITTED	DIFFERENCE B_1 (INCREASE)	DIFFERENCE B_2 (DECREASE)	P
1	30	4	+0.8	−0.5	<0.005
2	94	9	+1.3	−0.2	<0.005
3	140	6	+0.9	−0.2	<0.005
4	50	6	+2.4	−0.6	<0.005
5	94	6	+1.1	−0.3	<0.005
6	98	5	+1.2	−0.3	<0.005
7	54	4	+0.8	−0.7	<0.005
8	30	4	+1.5	−0.1	<0.005

B_1 = Average difference between threshold values obtained at noon and 1:30 P.M. on days on which lunch had been ingested. B_2 = on days on which lunch had been omitted. P = Probability that differences B_1 and B_2 are not significantly different from each other.

meal and a statistically significant increase during the later afternoon. In 2 of the remaining subjects, *subject 55* and *subject 56*, the increase in olfactory acuity during the later afternoon was demonstrable though not of significant magnitude. In one, *subject 57*, the increase in olfactory acuity during the morning failed to be of significant magnitude. In the one remaining subject, *subject 58*, the average threshold values indicated the existence of an increase in olfactory acuity during the morning, of a decrease shortly following ingestion of lunch and of another increase during the later afternoon; however, none of these variations in olfactory acuity was found to be of significant magnitude. The decrease in olfactory acuity shortly following the ingestion of noon meals was found to be of significant magnitude in 57 of the 58 subjects.

The significance of the decrease in olfactory acuity noted shortly after ingestion of noon meals may be deduced also from the analysis of results obtained on days on which noon meals had been omitted. This analysis shows for

all subjects so tested that changes in olfactory acuity observed after lunch time on days on which lunch had been ingested differed significantly from those observed at the same time of the day but on days on which lunch had been omitted. The conclusion may be drawn that ingestion of freely selected meals is followed by a significant decrease in olfactory acuity.

The results here subjected to analysis represent information assembled from investigative work performed in this laboratory by six assistants during the past three years. Method and procedure employed in the studies yielded results of remarkable similarity although obtained by different assistants. Thus comparable results were obtained when tests had been performed in a subject by different assistants. Thorough familiarity with method and procedure acquired over the years made it possible to minimize experimental errors and frequently to explain exceptional results. Certain thoughts and observations pertinent to the point appear worthy of mention.

In selecting subjects for the present investigation it was found necessary to exclude individuals whose history revealed existence of chronic disease or of unusual food habits. Acute illness, particularly acute infections of the upper respiratory tract necessitated temporary exclusion of subjects from the group. Repeated examinations on test days of the subjects' nasal passages revealed often a decrease in patency during the latter part of the day, which may partly explain the failure occasionally noted of olfactory threshold values to decrease during the later afternoon. Also, general fatigue of the subjects as well as physical and emotional strain were noted to influence olfactory acuity. On test days the subjects were observed closely in order to make certain that they refrained from taking food or coffee and from using chewing gum between meal times. The subjects were permitted to smoke though not within a 15-minute period prior to tests. Individuals using drugs regularly (particularly those applied locally to the nasal mucous membrane) could not participate in the investigation. Also, excluded from the group were individuals frequently exposed to certain odors, particularly those of formalin and fat solvents. That certain drugs and odors may affect olfactory acuity has been shown previously by Elsberg and co-workers (5). In order to demonstrate temporary influences of meals upon olfactory acuity it was necessary to determine olfactory threshold values at short and uniform intervals before and after ingestion of the meals. This consideration was regarded important, particularly with respect to the first threshold determinations after breakfast because the threshold values obtained at this time served as points of reference for calculating changes in olfactory acuity occurring during the day. The occasional failure to demonstrate an increase in olfactory acuity during the morning hours may have been caused in part by failure to observe properly that precaution. In general, it can be stated that following several test days devoted to familiarizing the subject with the procedure and the assistant with the subject, the threshold values of the sub-

jects obtained in the morning became remarkably constant varying in magnitude from day to day by not more than 0.5 cc. of odorous air. It is considered beyond the scope of the present report to discuss the observation that individual differences exist with respect to levels of olfactory acuity. Suffice it to say that age and sex of the subjects did not seem to be of influence upon olfactory acuity as determined by the procedure described. It may be mentioned, however, that hyperacuity of olfaction was often noted to exist during one or two days preceding the onset of menstrual periods.

In previous reports from this laboratory the suggestion has been made that the conversion of the sensation of appetite into one of satiety brought about by ingestion of food may be characterized by a concomitant decrease in olfactory acuity. If this assumption should prove to be correct, the occasional failure to demonstrate a significant decrease in olfactory acuity following ingestion of the noon meals may have to be explained in part by a failure of the meal to produce a sensation of satiety. Although statements of the subjects in regard to their sensations before and after meals were recorded, it is difficult to subject to analysis statements of this type. The impression was gained, however, that meals which failed to produce a decrease in olfactory acuity also failed to produce a sensation of satiety.

The above remarks were not intended to enumerate all possible sources of error inherent in method and procedure employed in the present investigation. Only those sources of error have been mentioned which were considered of utmost importance and considered to be avoidable.

SUMMARY

An analysis is presented of results obtained from studies concerning the existence in normal individuals of diurnal variations in olfactory acuity.

The following conclusions appear warranted. Taking into account averages of olfactory threshold values obtained on 9 or more test days, there are to be expected a significant increase in olfactory acuity during the morning, a significant decrease in olfactory acuity shortly after ingestion of freely selected noon meals and a significant increase in olfactory acuity during the later afternoon. The number of individuals studied justifies the expectation that similar results may be obtained from the population at large. The variations in olfactory acuity described appear to be intimately related to food intake because they fail to occur when noon meals are omitted. Brief mention was made of possible sources of experimental errors.

ADDENDUM

While the present report was being prepared a paper on the subject matter was published by Janowitz and Grossman (6). In their communication these authors claimed to have ruled out the existence in normal individuals of diurnal

variations in olfactory acuity. Their claim is based upon results obtained from olfactory threshold determinations performed in 17 subjects on 27 days. Eleven of these subjects were tested on one day, two of the subjects on two days and four of the subjects on three days. The description of method and procedure followed for determining olfactory thresholds conveys the impression that the authors had failed in their investigation to observe certain precautions essential for ensuring reliability of results. The observation that individual olfactory acuity levels seemingly varied widely from day to day likewise may be interpreted as indicating unreliability of the data presented. In addition, for reasons previously discussed, the authors' choice for subjects of medical and graduate students working in or near certain laboratories must be considered improper.

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Mechanical Efficiency in Cycling of Boys Seven to Fifteen Years of Age[1]

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MANY STUDIES of the mechanical efficiency of adults have been reported but to date little work has been done with children and none at all with young children. The object of this paper is to present the results of determining the mechanical efficiency of 19 boys 7 to 15 years of age by means of a bicycle ergometer of electric brake type patterned after those designed by Benedict and Carpenter (4), Benedict and Cady (5) and Krogh (6). A diagram of the open circuit respiration chamber showing the bicycle ergometer in place will be found in a paper from this laboratory by Taylor *et al.* (7) reporting the energy expenditure by these boys for sitting quietly and for cycling.

BICYCLE ERGOMETER

The bicycle ergometer consists of a bicycle frame mounted on supports with the rear wheel replaced by a copper disk, 40.7 cm. in diameter, mounted on a transverse shaft on ball bearings in firm supports. On the same shaft a rotating magnetic core is mounted on ball bearings. This is made of Swedish iron and supports 4 field coils in such a manner that the copper disk rotates between the pole faces of the coils. To prevent too rapid acceleration of movement of the core, a telescoping arm with a roller at the end is fastened to the under side of the core and rolls on the surface of an arc. Regulation sprocket, chain and pedals are used to rotate the disk.

To measure the work done a half-kilogram weight is suspended from the end of a torque arm placed at right angles to the magnetic core and equal in length to the radius of a 2-meter circle. By passing a constant current of 0.6 ampere through the coils a magnetic field is set up which acts as an electric brake to oppose the rotation of the copper disk. As the disk rotates the half-kilogram weight is lifted to balance the effect of the brake and thus with each revolution of the disk, work equivalent to one kilogram-meter is done.

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[1] Data in this paper are from dissertations submitted by Clara M. Taylor (1), Mary E. Robertson (2) and Mina W. Lamb (3) in partial fulfillment of requirements for the degree of Doctor of Philosophy, under the Joint Committee on Graduate Instruction, Columbia University, New York City.

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The boys sat upright throughout the tests, this being the position in which most children ride. The handle bars were movable enabling the boys to approximate the arm motions ordinarily brought into play when riding in the open. The height of the saddle was always carefully adjusted to insure comfort and to avoid the necessity for any extra energy expenditure due to stretching of legs and feet to reach the pedals. The number of revolutions of the copper disk was recorded by an electric cyclometer located on the control board outside the chamber and operated by a photoelectric cell.

The total work done by the cyclists consisted of 2 components, the work done in lifting the half-kilogram weight and the work done against the mechanical friction of the ball bearings, chain and telescoping roller. In order that approximately the same amount of work should be done in each test period, red and green lights were placed on a support just below the handle bars, where they were easily seen by the cyclists, and connected with contacts on the rear support. If the pedaling was too fast, the red light showed, if too slow, the green light. The contacts were set for the desired speed and the boys instructed to pedal just fast enough to keep both lights out. This proved to be a satisfactory means of maintaining a speed of 54 to 65 pedal revolutions per minute. Similar red and green lights placed on the control board outside the chamber and operated simultaneously with those on the bicycle kept the observer informed as to the regularity of the pedaling.

The ergometer was calibrated[4] by measuring the amount of work done in pedaling against the total load. A motor was attached by means of a chain to a special sprocket mounted on the axis of the pedals and the ergometer driven at speeds of 48 to 81 revolutions per minute. The power expended in driving the motor, which in turn drove the ergometer, was measured by a voltmeter-ammeter combination. Having determined the power needed to drive the motor separately, the power required to drive the ergometer was obtained by difference. This power, measured in watts, was converted into kilogram-meters of work done for each speed within the aforementioned range for a given time and included both the work done in lifting the weight and that done against friction. Knowing the work done in lifting the weight, that done against friction was obtained by difference. From a curve constructed by plotting the work done against friction in 15 minutes against the revolutions of the copper disk in the 15-minute period, the work done against friction corresponding to the observed number of revolutions of the copper disk could be read directly.

PROCEDURE

Except in *Group II* the results reported are those of tests made in the afternoon after school, $3\frac{1}{2}$ to 4 hours after a light to moderate meal. In *Group*

[4] The work of George J. Dzwons, engineer, in carrying out this calibration is gratefully acknowledged.

II the results of tests made in the morning before breakfast are averaged with those made after school, Taylor (1) having established the fact, by making 17 tests before breakfast and 29 after school, that the differences between the results were so small as to be negligible. It was also established, as the result of 15 tests on each of the three groups, that cycling at the rate of 49 to 69 revolutions per minute did not cause oxygen debt. Therefore, no recovery period was required.

As in the determinations of the energy expenditures for sitting quietly and cycling already reported (7), two boys were studied at a time and treated as one subject, the same boys being paired each time. The chamber was thoroughly ventilated before each test and the ventilation continued for 5 minutes after the boys had entered the chamber and the door had been closed. Then followed a 15-minute period of sitting quietly on a chair after which the boys were given the signal to start cycling. Except in *Group I* each boy pedaled for 15 minutes, the other boy continuing to sit quietly. Thus a total of 30 minutes of cycling was obtained. In *Group I* it was found that a 15-minute cycling period was too long, but when the time was divided so that each boy in turn rode for 8 minutes and then for 7 minutes, making a total of 15 minutes each, a total of 30 minutes was easily obtained.

The increase in the carbon dioxide content of the chamber air was determined by analyzing samples of air withdrawn from the chamber through a small opening provided for that purpose at the beginning and end of each experimental period. For these analyses the Carpenter modification of the Haldane gas analysis apparatus was used. These results were corrected for the amount of carbon dioxide in the outdoor air circulated through the chamber during the period. The absorbing trains, of which there are two, enabling the observer to change from one to the other without any break between successive periods, were weighed before the beginning and at the end of each period. The increase in weight, corrected for the carbon dioxide of outdoor air, could then be added to the corrected carbon dioxide of the chamber air to obtain the total carbon dioxide production. The average carbon dioxide production per boy while cycling was obtained by subtracting from the total carbon dioxide produced during the 30-minute cycling period the average carbon dioxide produced per boy sitting quietly for 30 minutes. From the carbon dioxide production per boy thus obtained the cost of the work done was calculated.

At frequent intervals, usually once a week, the chamber and absorbing trains were tested for tightness by determining the percentage recovery of known weights of carbon dioxide introduced. The average percentage recoveries of the weekly tests were 99.9, 99.5, and 99.5 for *Groups I*, *II*, and *III*, respectively.

MECHANICAL EFFICIENCY

The mechanical efficiency of the body is expressed in a number of different ways. The term 'gross efficiency' is commonly used to express the relation between the work done and the total energy expended in performing it, while the term 'net efficiency' is applied to the relation between the work done and the energy expended in doing the work over and above that required to maintain the body in the 'resting position.' The term, resting position, as found in the literature of bicycle ergometer studies, has several meanings. In some studies it is taken to mean the position maintained when the subject is sitting on the bicycle, in others the resting position is taken as that of the subject sitting on the bicycle and pedaling without a resistance load, often spoken of in the reports as 'coasting.' In other studies the resting position is that of the subject sitting on the bicycle and pedaling while the pedals are turned by a motor and in still other studies the energy expended for resting position is considered to be that expended by the subject under basal metabolism conditions.

TABLE 1. AVERAGE ENERGY EXPENDITURE FOR BASAL METABOLISM AND SITTING QUIETLY

	BASAL METABOLISM *Cal/boy/hr.*	SITTING QUIETLY[1] *Cal/boy/hr.*
Group I	42.9	69.1
Group II	45.9	72.5
Group III	53.2	86.6

[1] Including the basal metabolism.

Active 7- to 15-year-old boys could not be expected to sit quietly on the bicycle for a long enough period to measure the energy expended in this resting position without building up considerable muscle tone from annoyance as well as from restlessness. Neither was it considered practical to determine for a base line the energy expended by the subjects when the pedals were rotated by a motor and the legs allowed to swing idly with the pedals. Instead of either of these base lines it was thought better to substitute the energy expended by the boys sitting quietly reading or playing with simple puzzles or toys involving the use of only the finger muscles. Net efficiency was also calculated using the basal metabolism as a base line. The average energy expenditure for basal metabolism and sitting quietly is given for each group in table 1.

RESULTS AND DISCUSSION

The average results of the determinations of mechanical efficiency are given in table 2. The smallest coefficient of variation in each group is that for the gross efficiency, while that for the net efficiency calculated after deducting the energy cost of sitting quietly is the highest. This higher coefficient of variation may well be due to the fact that small differences in the additional energy

expenditure for the bicycle riding show up as large differences when the expenditure for sitting quietly is deducted from the total expenditure for cycling. Also it is true that the coefficients of variation for sitting quietly, as reported by Taylor *et al.* (7), are larger than those for cycling, doubtless due to the activity being more controlled in the cycling period. When we consider the natural variability in the involuntary movements of the boys from day to day coefficients of variation ranging from 7.9 to 13.3 per cent for gross efficiency, from 10.3 to 14.8 per cent for net efficiency with basal metabolism deducted, and from 15.7 to 21.8 per cent for net efficiency with the energy cost for sitting quietly deducted, these results seem not too great to be acceptable. The validity of the results is indicated by the values 0.6 to 3.6 obtained when the probable errors are expressed as percentage of their means.

TABLE 2. AVERAGE RESULTS OF DETERMINATIONS OF MECHANICAL EFFICIENCY

GROUP	AGE RANGE	TOTAL WORK DONE/BOY/HR.	COST OF TOTAL WORK DONE/ BOY/HR.	EFFICIENCY—PER CENT		
				Gross	Net	
					Basal Metabolism Deducted	Metabolism for Sitting Quietly Deducted
	year month	*Cal.*	*Cal.*			
I	6 9	19.2±0.2	147.3±2.4	13.0±0.2	18.4±0.4	24.6±0.9
6 Subjects	to	C.V. = 7.1%	C.V. = 10.2%	C.V. = 9.9%	C.V. = 11.9%	C.V. = 20.7%
18 Tests	8 7	P.E. = 1.0% of Mean	P.E. = 1.6% of Mean	P.E. = 1.5% of Mean	P.E. = 2.1% of Mean	P.E. = 3.6% of Mean
II	9 6	23.3±0.1	148.1±1.4	15.7±0.1	22.8±0.3	30.8±0.6
6 Subjects	to	C.V. = 4.5%	C.V. = 8.5%	C.V. = 7.9%	C.V. = 10.3%	C.V. = 15.7%
35 Tests	11	P.E. = 0.4% of Mean	P.E. = 0.9% of Mean	P.E. = 0.6% of Mean	P.E. = 1.3% of Mean	P.E. = 1.9% of Mean
III	12 5	24.4±0.4	189.5±3.9	12.9±0.2	17.9±0.4	23.7±0.7
7 Subjects	to	C.V. = 11.7%	C.V. = 14.9%	C.V. = 13.3%	C.V. = 14.8%	C.V. = 21.8%
24 Tests	15 1	P.E. = 1.6% of Mean	P.E. = 2.1% of Mean	P.E. = 1.5% of Mean	P.E. = 2.2% of Mean	P.E. = 2.4% of Mean

It must be borne in mind that mechanical efficiency varies with speed, the external work performed, the training of the subjects, the duration of the work period, diet and the base lines used in determining the net efficiency.

The average number of pedal revolutions by the boys of *Groups I* and *II* was 57, that for the boys of *Group III*, 65. These figures fall well within the range of speeds considered by other investigators to be most efficient. Garry and Wishart (8), experimenting with speeds ranging from 25 to 98 pedal revolutions per minute, found the optimum gross efficiencies for two untrained subjects at a speed of 52. Benedict and Cathcart (9), testing subjects at speeds ranging from 54 to 128 pedal revolutions per minute, found the maximum efficiency at 70, a speed below which their professional cyclist preferred not to pedal. Dickinson (10), out of a range of speeds from 8 to 60 pedal revolu-

tions per minute, obtained the highest efficiency at 33. Amar (11) observed a rise in efficiency as the speed increased from 70 to 90 pedal revolutions per minute but a decrease at 100 revolutions per minute. Briggs (12), in a study of Scottish soldiers, found 56 revolutions per minute to be the most comfortable speed.

TABLE 3. COMPARISON OF RESULTS OF THESE STUDIES WITH THOSE OF COMPARABLE STUDIES OF MECHANICAL EFFICIENCY DURING CYCLING

SUBJECTS	NO. OF SUBJECTS	NO. OF TESTS	PEDAL	WORK DONE	EFFICIENCY—PER CENT		REFERENCE
					Gross	Net	
			rev/min.	*Cal/min.*			
Boys							
7 to 9 yr.	6	18	57	0.32	13.0	18.4[1]	This study
						24.6[2]	
9 to 11 yr.	6	35	57	0.39	15.7	22.8[1]	This study
						30.8[2]	
12 to 15 yr.	7	24	65	0.41	12.9	17.9[1]	This study
						23.7[2]	
14 yr.	1	37	60	0.7–0.8		22.4[3]	(16)
Men							
"	2	4	68	0.46	10.3	13.8[1]	(9)
"	7	16	73	0.48	12.2	17.2[1]	(3)
						21.7[2]	
"	3	9	60	0.50		20.9[3]	(13)
"	2	2	70	0.51	9.5	23.8[4]	(8)
"	2	14	60	0.68		22.9[3]	(13)
"	2	3	59	0.83		20.9[1]	(4)
"	3	17	60	0.88		22.9[3]	(13)
"	1	2	56	0.98		19.4[3]	(9)
"	2	3	58	1.01	15.5	18.5[1]	(9)
"	1	8	60	1.08		21.9[3]	(13)
"	2	4	61	1.48	16.2	19.5[3]	(8)
						26.1[4]	
"	1	13	60	1.66		22.3[3]	(13)
"	1	2	60	2.06		21.0[3]	(13)
"	2	9	58	2.75		17.6[3]	(17)

[1] Base line, basal metabolism [2] Base line, sitting quietly [3] Base line, sitting on bicycle
[4] Base line, subject pedaling with no load (without motor).

The average total work done by the boys of the three groups ranges from 19.2 to 24.4 Cal. per hr. This narrow range is explained, of course, by the fact that the load against which the cycling was done was the same in all the tests, as was also the duration of the work period.

Although some of the boys owned bicycles they did not have opportunity to use them much and consequently they were all considered untrained subjects. As each pair of boys seldom served as subjects oftener than once a week and the work performed was not strenuous enough to demand great effort on their part, it is not surprising that no evidence of any influence of training was seen during the progress of the tests.

The influence of diet on efficiency is reported in a number of studies in the literature. Reynolds, Sevringhaus and Stark (13) found that the net efficiency of their 3 subjects in cycling (energy expenditure for sitting on the bicycle deducted) ranged from 21 to 24 per cent regardless of whether the diet was high in carbohydrate, high in fat or an average mixed diet. Marsh and Murlin (14), measuring efficiency on a bicycle ergometer, obtained results ranging from 19.7 to 24.0 per cent on a normal diet. The efficiencies on other types of diet which they used fell within this range. Haldi *et al.* (15) found the same net efficiency (metabolism for lying at rest deducted) whether their subjects ingested glucose or fructose or a mixture of these sugars or an average breakfast before cycling. The boys who served as subjects in this investigation were living on a good institutional diet and most of the tests were made after school in the afternoon $3\frac{1}{2}$ to 4 hours after the last intake of food, it having been established at the beginning of the study that tests at this time gave results in agreement with those obtained in determinations made before breakfast. Influence of diet on the efficiency, therefore, was not a factor.

The only determination of the mechanical efficiency of children by means of the bicycle ergometer found in the literature is that of Marsh (16) who, in connection with a study of the character of energy metabolism during work, reported an average net efficiency (expenditure sitting on the bicycle deducted) of 22.4 per cent for a 14-year-old boy; gross efficiency was not given.

The results of our studies on boys 7 to 15 years of age are given in table 3 along with those of Marsh and of some comparable investigations on untrained men.

The gross efficiencies when the men and boys performed the same amount of external work are higher for the boys than for the men, but when the men performed approximately three times as much external work as the boys, the gross efficiencies of men and boys are of the same order of magnitude. Benedict and Cathcart (9) found that the efficiency of their men subjects increased as the load increased from small to moderate but decreased with still greater loads.

When net efficiency is calculated with the basal metabolism deducted, the average for the three groups in this study is 19.7 per cent (range, 17.9–22.8), while that for the men reported on this base line is 17.6 per cent (range, 13.8–20.9), a difference of 2.1 per cent. The average net efficiency of the boys calculated after deducting the expenditure for sitting quietly is 26.4 per cent (range, 23.7–30.8). If this is compared with those cases in which the base line was sitting on the bicycle, we find the result of 22.4 per cent for Marsh's boy, while the average of nine reports on men on this base line is 20.9 per cent (range, 17.6–22.9). The two reports on men when the base line was that of pedaling with no load give an average net efficiency of 25.0 per cent. The one report of net efficiency of men when the base line was that of sitting quietly on a chair gives a result of 21.7 per cent.

SUMMARY

Seventy-seven determinations of the mechanical efficiency of 19 boys, 7 to 15 years of age, are reported. The work was measured by means of a bicycle ergometer of electric brake type in a respiration chamber. The results are reported as gross efficiency, net efficiency after deducting the basal metabolism, and net efficiency with the energy expenditure for sitting quietly on a chair deducted. Eighteen determinations on 6 boys, 7 to 9 years of age, gave an average gross efficiency of 13.0 per cent, an average net efficiency with basal metabolism deducted of 18.4 per cent, and an average net efficiency with cost of sitting quietly deducted of 24.6 per cent. Thirty-five determinations on 6 boys, 9 to 11 years of age, gave an average gross efficiency of 15.7 per cent, an average net efficiency with basal metabolism deducted of 22.8 per cent, and an average net efficiency with cost of sitting quietly deducted of 30.8 per cent. Twenty-four determinations on 7 boys, 12 to 15 years of age, gave an average gross efficiency of 12.9 per cent, an average net efficiency with basal metabolism deducted of 17.9 per cent, and an average net efficiency with cost of sitting quietly deducted of 23.7 per cent.

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Correlation of Acid, Pepsin and Mucoprotein Secretion by Human Gastric Glands

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STUDIES CORRELATING ACID AND PEPSIN SECRETION in the stomach with quantitative estimations of mucin have not been altogether satisfactory owing to the fact that total mucin determinations measured only the algebraic sum of a mixture of not necessarily related components. Thus there appeared to be no correlation of mucin values with other indicators of gastric function. Since the recent development of a method for the separate determination of the glandular product (mucoprotein) from other constituents of gastric mucin (visible mucoid and mucoproteose), it has become feasible to assess the relationship of mucoprotein to other important secretions of the gastric glands (1–3).

This communication reports a simultaneous quantitative study of all three secretory products of gastric glands, acid, pepsin and mucoprotein under fasting conditions and after central vagus stimulation in the form of intravenously administered insulin.

MATERIAL AND METHODS

The data on fasting secretion were derived from 37 subjects with normal and diseased stomachs from whom one or more fasting specimens were obtained (total of 61 specimens). Eight of these subjects were tested before and after either gastric resection or vagotomy.

All fasting secretions were collected at least 12 hours after the last meal. Contamination by saliva and sputum was minimized by providing the subject with a sputum bottle and instructing him not to swallow. The first fasting specimen was obtained by evacuating the stomach as completely as possible through a Levine tube and 20 minutes thereafter the second fasting specimen was aspirated.

Twenty-four subjects with normal and diseased stomachs were subjected to the intravenous insulin test. Some of these individuals were tested both before and after vagotomy or gastric resection (total of 30 tests). The insulin tests were performed in the standard manner (4–7). After complete aspiration of two fasting specimens 16 U of insulin was injected intravenously and gastric speci-

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TABLE 1. ANALYSES OF 61 FASTING GASTRIC CONTENTS OF 34 INDIVIDUALS

TEST NO.	CASE NO.	DIAGNOSIS	VOLUME	GASTRIC ACIDITY		GASTRIC MUCOPROTEIN	PEPSIN UNITS	CONTAMINATION
				Free	Total			
			cc.	*mEq/l.*		*mg/100 cc.*	*P.U.* $\frac{Hb}{10}$ ×	
1	9	Normals and 'nervous indigestion'	27	58	64	81	51	
2	11		17	11	27	98	101	
3	12		42	62	75	165	162	
4	16		8	8	25	136	114	
5	24		11	0	14	Trace[1]	0	
6	25		12	0	10	Trace	0	
7	6		5	14	28	Trace	27	
8	26	Duodenal ulcer	32	65	84	250	425	
9	1		33	0	27	Trace	114	
10	1		27	0	24	Trace	150	
11	2a[2]		45	7	18	65	105	
12	2a		78	23	33	81	122	
13	3a		27	32	47	81	168	
14	3a		14	50	63	86	98	
15	4		107	7	16	47	53	
16	4		76	16	26	81	80	
17	7a		35	29	26	57	50	
18	8		12	16	28	163	23	
19	10a		87	28	35	65	110	
20	34a		20	44	55	69	60	
21	22a		14	0	16	Trace	54	
22	22a		21	9	25	Trace	48	
23	36		85	36	45		71	
24	36		36	50	62		91	
25	13	Gastric ulcer	42	0	5	Trace	20	
26	13		28	0	6	Trace	21	
27	27		30	15	34	97	98	
28	28		107	16	30	148	163	
29	28		35	0	6	Trace	51	
30	5a	Pyloric stenosis due to ulcer	52	33	51	110	116	Food + +
31	5a		45	48	64	114	117	Food + +
32	29		300	56	86	111	211	Food + +
33	30		20	0	10	Trace	4	Food +
34	31	Atrophic gastritis	24	0	11	Trace	35	
35	32		8	0	11	Trace	30	
36	33		5	0	3	57	5	
37	17	Tumors of the stomach	3	0	3	Trace	0	
38	17		4	0	4	20	0	
39	14a		30	0	2	Trace	0	Bile + + +

TABLE 1. (*Continued*)

TEST NO.	CASE NO.	DIAGNOSIS	VOLUME	GASTRIC ACIDITY		GASTRIC MUCOPROTEIN	PEPSIN UNITS	CONTAMINATION
				Free	Total			
			cc.	*mEq/l.*		*mg/100 cc.*	$P.U._{10^4}^{Hb} \times$	
40	5b[2]	Subtotally resected stomach	17	0	7	0	0	Bile +
41	18		26	0	10	28	21	
42	18		38	0	10	Trace	0	Bile + +
43	19		35	0	7	Trace	0	Bile + +
44	19		40	0	6	Trace	0	Bile + +
45	20		6	0	9	Trace	0	
46	21		11	0	3	Trace	0	
47	21		16	0	3	Trace	0	
48	35		3	0	3	Trace	0	
49	22b		10	0	5	Trace	34	
50	2b		30	0	2	85	0	
51	2b		65	0	2	96	0	
52	23		65	0	8	Trace	0	Bile + +
53	23		23	2	13	78	0	Bile + + +
54	14b		27	0	6	Trace	0	Bile + + +
55	14b		14	0	6	Trace	0	Bile + + +
56	7b	Vagotomized stomach	4	0	6	Trace	0	Bile + + +
57	10b		18	0	9	Trace	0	Bile + + +
58	10b		32	0	6	Trace	0	Bile + + +
59	34b		9	0	5	Trace	0	Bile + + +
60	34b		16	0	5	Trace	0	Bile + +
61	15		49	0	4	Trace	0	Bile + + +

[1] Trace = Mucoprotein concentration below 15 mg/100 cc. gastric juice. For computation this value was arbitrarily accepted as equal to 10 mg/100 cc.

[2] *a* = before operation; *b* = same case after operation

mens were collected 20, 40, 60 and 90 minutes after injection. In all specimens the concentrations of hydrochloric acid, pepsin and mucoprotein were determined.

Acidity was determined in the usual way by titration with Toepfer reagent and phenolphthalein. Gastric mucoprotein was determined by the colorimetric method of Glass and Boyd (1), and in the case of bile contamination by its volumetric modification (4, 5). Pepsin was determined by a modification of the Anson-Mirsky hemoglobin method described elsewhere (8).

Although precautions against possible contamination by saliva were taken as described above, it was not possible to eliminate completely this source of error. The error would be attributable almost entirely to dilution of the gastric juice since saliva contains no mucoprotein (1). The presence of the stomach tube may have had an effect on gastric secretion but this would have been a constant error since the tube was left in place throughout the procedure.

These data are presented in table 1. It will be noted that in those specimens from which free acid was absent, mucoprotein was also either absent or present in only very small amounts. Likewise, in most of the anacid specimens pepsin concentration was relatively low. This was most striking in specimens from those subjects who had undergone vagotomy or partial gastric resection. The correlation between low values for pepsin and acid, and pepsin and mucopro-

TABLE 2. RATIO OF CONCENTRATIONS OF MUCOPROTEIN TO PEPSIN IN 64 ACID SPECIMENS OF GASTRIC JUICE COLLECTED IN 24 INDIVIDUALS UNDER FASTING CONDITIONS AND AFTER I.V. ADMINISTRATION OF 16 U INSULIN

CASE NO.	SPECIMEN NO.	MUCOPROTEIN[1]: PEPSIN IN GASTRIC JUICE	CASE NO.	SPECIMEN NO.	MUCOPROTEIN[1] PEPSIN IN GASTRIC JUICE
	Fasting Gastric Contents			*Gastric Contents after Insulin Stimulation*[2]	
9	1	4.4	1	25, 26	2.0, 2.6
11	2	2.7	2	27, 28, 29	6.2, 1.7, 1.4
12	3	2.9	3a	30, 31, 32, 33	2.6, 1.5, 1.6, 3.1
16	4	3.3	4	34, 35, 36, 37	1.9, 3.6, 3.0, 2.6
6	5	1.0	7a	38, 39, 40	0.4, 2.4, 3.0, 3.1
26	6	1.7	8	41, 42, 43	0.4, 2.5, 2.4
2a	7, 8	1.7, 1.9	10a	44, 45, 46	1.0, 3.9, 2.7
3a	9, 10	1.3, 2.5	34a	47, 48	2.6, 1.8
4a	11, 12	2.5, 2.8	22a	49, 50, 51	2.1, 2.7, 2.6
7a	13	3.2	5a	52, 53	1.4, 1.4
8	14	20.0	37	54, 55, 56	1.4, 1.4, 1.1
10a	15	1.7	6	57, 58, 59	2.2, 3.3, 2.4
34a	16	3.2	18	60	4.2
22a	17	0.6	20	61	4.1
36	18, 19	0.4, 0.3	23	62, 63	mucoprotein: 74 and 10 mg., in absence of pepsin
27	20	2.8			
28	21	2.5			
5a	22, 23	2.7, 2.7			
29	24	1.5			

[1] Both concentrations were calculated in mg/100 cc. gastric juice.

[2] Several values reported in each case refer to several specimens collected after i.v. administration of 16 U insulin.

tein is less uniform than that for low values of mucoprotein and acid. In certain instances (mainly in duodenal or gastric ulcer) relatively high concentrations of pepsin were detected in the absence of free acid and with very low mucoprotein concentration.

On most occasions when free acid values were relatively high (above 40), mucoprotein concentration (between 70 and 250 mg.%) as well as pepsin (between 50 and 425 U) was also high. Apart from the relatively gross correlations mentioned, no parallelism was noted among the three products of the gastric glands either in normal, diseased or partly resected stomachs.

Table 2 gives ratios of mucoprotein to pepsin in 64 of the gastric specimens

collected from 24 individuals before and after insulin stimulation. Specimens, the titratable free acid of which was 5 mEq/liter or lower, were omitted because of the possibility of pepsin inactivation at a comparatively high pH. To calculate these ratios, the concentration of both substances was expressed in mg/100 cc., pepsin having been calculated in terms of crystalline pepsin of a specific activity $P.U.^{Hb} = 0.184$ (8–10). It will be noted that there is no quantitative relationship between the two measured compounds.

Earlier workers have pointed out a close relationship between pepsin and mucoprotein (11–14) with regard to some of their physical properties, crystalline structure and the response of the cells producing them to neural and humoral stimuli.

Despite similarities it has been shown that mucoprotein contains a moiety of hydrolyzable polysaccharide not present in pepsin and that the isoelectric point of mucoprotein (3.5 to 4) (2) differs from that of pepsin (2.7). Moreover, pepsin has been shown to have a higher nitrogen content than mucoprotein (2) and to be soluble in a concentration of acetone (60%) (15) which precipitates mucoprotein (1).

The disparity in concentration between mucoprotein and pepsin observed in the experiments detailed above is further evidence that pepsin and mucoprotein, while possibly related, are certainly not identical substances. It seems clear that they can be secreted independently of each other. These findings confirm the recent observations of Grossberg, Komarov and Shay (16) who used different chemical methods.

a) Pepsin and Mucoprotein. Further data on the relationship of pepsin and mucoprotein were advanced from the analysis of gastric juice after insulin injection. It was evident that no one-to-one correlation existed between the concentration of these products. In fact, at times a relatively wide disparity was recorded between the values obtained for pepsin and mucoprotein in the same subject during one experiment.

b) Patterns of Secretion of Acid, Pepsin and Mucoprotein. The data correlating all three products of the gastric glands following insulin injection are presented in table 3. They fall generally into three categories: *1*) Positive pattern characterized by an increase in concentration of pepsin, mucoprotein and free and total acid. Normal subjects and those with 'nervous indigestion' and pyloric and duodenal ulcer fell into this category. In figure 1 are shown curves of all three glandular products of the stomach after insulin stimulation. *2*) Dissociated pattern characterized by an increase in concentration of mucoprotein and/or pepsin without significant change in acid secretion (fig. 1). All of the subjects who had localized antral lesions (polyps, ulcer) and most of those who had undergone subtotal gastrectomy fell into this category as shown in table 3. *3*) Negative pattern characterized by absence of stimulating effect of insulin on any of the three gastric constituents meas-

TABLE 3. GASTRIC SECRETORY TESTS AFTER INSULIN STIMULATION

INSULIN TEST NO.	CASE NO.	DIAGNOSIS	VOLUME		FREE ACIDITY		TOTAL ACIDITY		GASTRIC MUCOPROTEIN		PEPSIN UNITS		PEPSIN	
			Fasting	After insulin 20 40 60 90 minutes	Fasting	After insulin 20 40 60 90 minutes	Fasting	After insulin 20 40 60 90 minutes	Fasting	After insulin 20 40 60 90 minutes	Fasting	After insulin 20 40 60 90 minutes	Fasting	After insulin 20 40 60 90 minutes
			cc.		*mEq/l.*		*mEq/l.*		*mg/100 cc.*		*P.U.*$^{Hb} \times 10^{1}$		*mg/100 cc.*	
1	1	Duodenal ulcer	30	40 52 30	0	0 28 74	27	10 56 96	Tr.[1]	25 158 151	132	28 221 160	47	10 79 57
2	22[2]		61	83 76 88	15	6 77 94	25	23 87 104	73	20 168 108	113	90 280 215	40	32 100 77
3	3a		21	79 29 88 160	41	53 73 101 63	55	69 82 112 72	84	80 88 102 72	133	86 161 183 65	47	31 57 65 23
4	4		91	30 96 31 48	12	38 110 118 110	21	52 117 127 112	64	186 271 180 130	66	280 210 170 140	24	100 75 61 50
5	7a		35	29 26 57 50	6	14 13 82 88	19	34 31 95 100	Tr.	Tr. 153 243 249	19	63 181 227 226	7	22 64 81 81
6	8		12	10 77 14	16	54 103 90	28	69 112 102	163	34 168 157	23	222 189 182	8	79 67 65
7	10a		87	35 59 58 61	28	20 31 92 92	35	30 40 100 101	65	86 144 115	55	20 160 105 120	20	7 57 37 43
8	34e		20	11 1 20 15	44	22 29 86 86	55	37 40 98 100	69	41 96 103	60	52 105 162	21	19 37 58
9	22a		18	22 22 29 26	5	10 72 94 103	20	40 84 110 117	Tr.	Tr. 135 144 115	50	64 175 149 122	18	23 62 53 43
10	36		60	40 71 82 102	43	33 74 100 87	53	41 84 110 98	111	67 189 169 115	81	79 154 158 126	29	28 55 56 45
11	13	Gastric ulcer	6	18 23 19	0	0 0 0	5	8 9 10	Tr.	Tr. 178 335	20	40 367 367	7	14 130 130
12	5a	Pyloric stenosis	48	50 10 35 135	41	44 94	57	59 107	112	92 116 180 143	117	228 285	42	81 102
13	14a	Polyp. s chr. gastritis	30	21 36 42	0	0 0 0	2	2 2 22	Tr.	Tr. Tr. 160	0	0 20 ?	0	0 7 ?
14	37	Pyloric stenosis		300 87 63		56 55		86 85		111 111 201		211 211 488		75 75 174
15	6	(Nervous indigestion)	5	3 13 11 20	14	24 37 60 76	28	40 56 70 90	Tr.	40 139 151 150	27	180 133 175	10	64 47 62
16	17	Gastric lymphosarcoma after resection	3	8 7 16	0	0 0 0	4	3 4 4	Tr.	51 89 Tr.	0	0 0 0	0	0 0 0
17	56	Subtotally resected stomach for gastro-duodenal ulcers	17	11 4 5	0	0 0 0	7	13 7 30	0	0 175 300	6	48 ? 388	2	17 ? 138
18	18		32	32 20 23	0	0 0 6	10	6 17 31	20	30 364 415	10	0 276 276	4	0 98 98
19	19		37	38 8 17	0	0 0 0	7	8 11 14	68	? 95 174	0	? 0 20	0	? 0 7
20	20		6	18 23 19	0	0 0 24	9	13 ? 33	Tr.	110 ? 110	0	80 ? 76	0	29 ? 27
21	21		14	35 40 10 23	0	0 0 0 0	3	7 10 7 18	Tr.	40 Tr. Tr. Tr.	0	0 70 ? 70	0	0 25 ? 25
22	23		44	25 27 12	0	0 40 98	10	7 80 115	39	Tr. 74 109	0	0 0 0	0	0 0 0
23	35		3	4 5 4	0	0 0 0	3	3 3 3	Tr.	Tr. Tr. Tr.	0	0 0 0	0	0 0 0
24	22b[2]		10	11 24 3 19	0	0 0 0 0	5	5 5 5 7	Tr.	Tr. 42 ? 64	0	0 0 0 0	12	0 0 0 0
25	2b		48	51 23 17 19	0	0 0 0 0	2	3 6 9 12	Tr.	Tr. 30 30 35	0	0 0 0 0	0	0 0 0 0

| | | |

to their respective concentrations. In the intact stomach, however, hyperacidity was generally accompanied by hypersecretion of both pepsin and mucoprotein. Conversely when no hydrochloric acid was present there was usually no mucoprotein although pepsin might be present in significant quantities. While pepsin and mucoprotein may be closely related in their chemical and physical properties the two are not identical but separate constituents of the gastric juice.

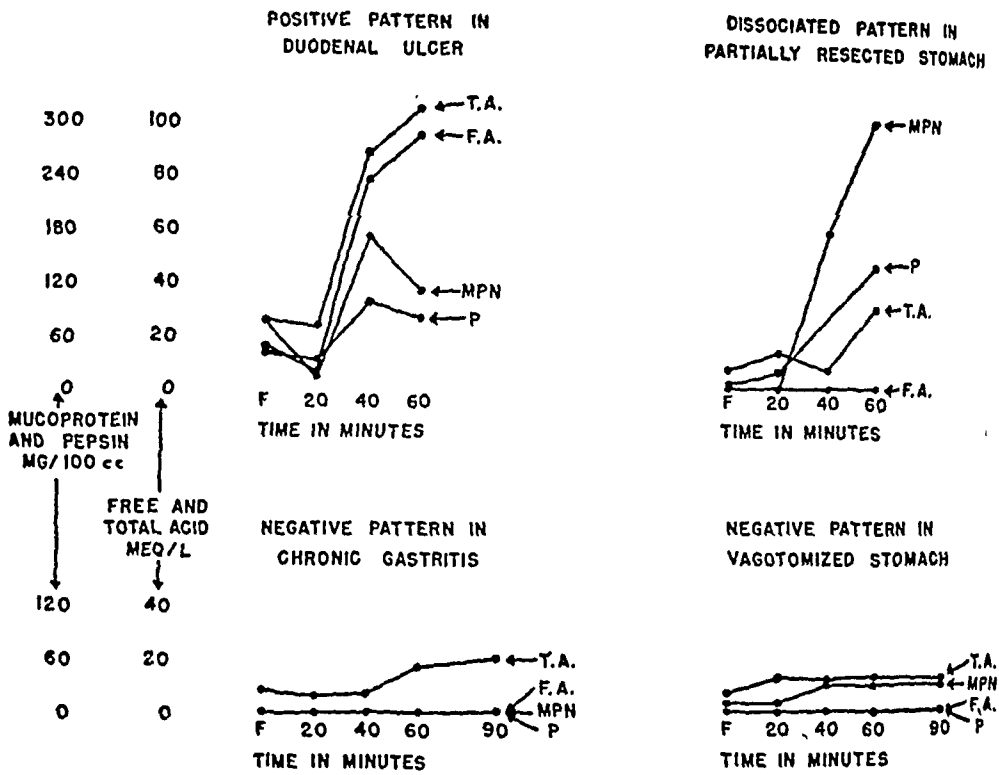

Fig. 1. SAMPLE EXPERIMENTS showing positive, negative and dissociated patterns of gastric secretion. *T. A.*=total acid. *F. A.* =free acid. *MPN*=mucoprotein. *P*=pepsin.

Following central vagal stimulation of the intact stomach by intravenously administered insulin, all three products of the gastric glands were elaborated in greatly increased concentration. In the presence of a diffuse inflammatory lesion and following bilateral vagotomy, insulin failed to stimulate the elaboration of any of the three products. A dissociated pattern of secretion following insulin, characterized by increased mucoprotein and/or pepsin without significant change in acid secretion, was recognized. It occurred chiefly following subtotal gastric resection and in the presence of antral gastritis, polyps or ulcers in the antral region. The failure of insulin under these circumstances to induce an increase in acid concentration accompanying the increase in pepsin and mucoprotein indicates that when the distal end of the stomach is damaged or absent the measurement of mucoprotein or pepsin would be more useful than acid as a test of intactness of vagus fibers.

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Effect of Variation in Swing Radius and Arc on Incidence of Swing Sickness[1]

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IT IS GENERALLY ACCEPTED that changes in the forces, acting through the longitudinal axis of the body, are a major factor in the production of motion sickness. It appeared desirable, therefore, to determine, if possible, the quality and quantity of these changes which are required to elicit the motion-sickness syndrome. It was felt that such an investigation might not only provide information of value in the prophylaxis of motion sickness, but might also help to elucidate the etiology of the condition.

Swings have been extensively used in the study of motion sickness, and they were selected for this work because they were particularly suitable for this investigation. The frequency of oscillation of a swing or pendulum is determined by the distance from the fulcrum. The quantity of the changes in this force acting in the longitudinal axis of the swing or pendulum is dependent on the angle through which the pendulum oscillates. Thus one may vary the frequency or the quantity of change in this force to which a subject is exposed on the swing, by varying the radius or arc, respectively.

METHODS

Two hundred and fifty unselected normal aircrew acted as subjects. These men were engaged in preliminary ground studies, prior to flying training. They had not been employed in any previous motion-sickness studies, and were informed that the results would in no way influence their medical category. They were swung in the sitting position, with eyes open, and with the head comfortably fixed so that the line joining the outer canthus of the eye and the external auditory meatus was perpendicular to the radius of the swing. Swinging was continued for 30 minutes unless extreme nausea and/or vomiting necessitated stopping before this time. The men were interviewed by a medical officer after their swing, and their response categorized as follows: Type III,

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severe nausea and/or vomiting; Type II, mild nausea and/or vomiting; and Type I, all others.

A specially built two-pole (single fulcrum) swing was used, which could readily be adjusted to a radius of 6, 10, or 16 feet. The total angles of oscillation used were 50, 90 and 130 degrees.

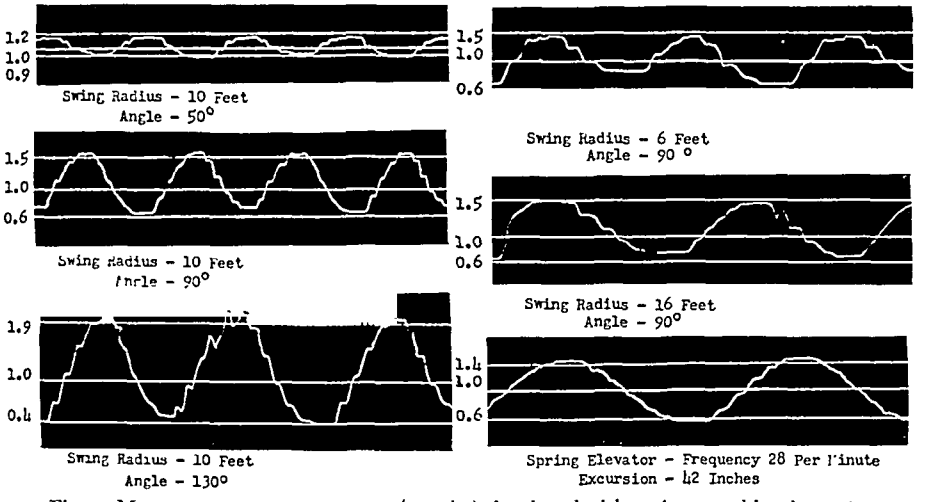

Fig. 1. MEASURED VERTICAL FORCES (g units) developed with various combinations of radius and amplitude of swing.

Each man was swung only once. The investigation extended over several weeks, as only 2 men could be swung per hour. The following sequence of experiments was maintained until 50 men were tested on each type of swing.

Radius *feet*	Angle *degrees*
1 to 16	90
2 to 10	130
3 to 10	90
4 to 10	50
5 to 6	90

By employing this sequence, errors in comparison, due to variation in time of day, ambient temperature, relation to meals, psychological factors etc., were minimized.

A simple spring accelerometer, similar to that described by Cipriani (1), was constructed and used to measure and record the relative changes in force acting radially, that is from head to foot, at the position of the ear of the subjects. The ears of the subjects were slightly removed from the center of gravity of the swing; this caused a slight difference between the two waves of a complete oscillation.

As is customary in this type of aviation physiology, measurements are expressed in units of acceleration rather than in units of force. Since mass remains constant, the relation between force and acceleration is constant. Values are expressed in units of g, the acceleration imparted to freely falling bodies by the earth's attraction (figs. 1 and 2).

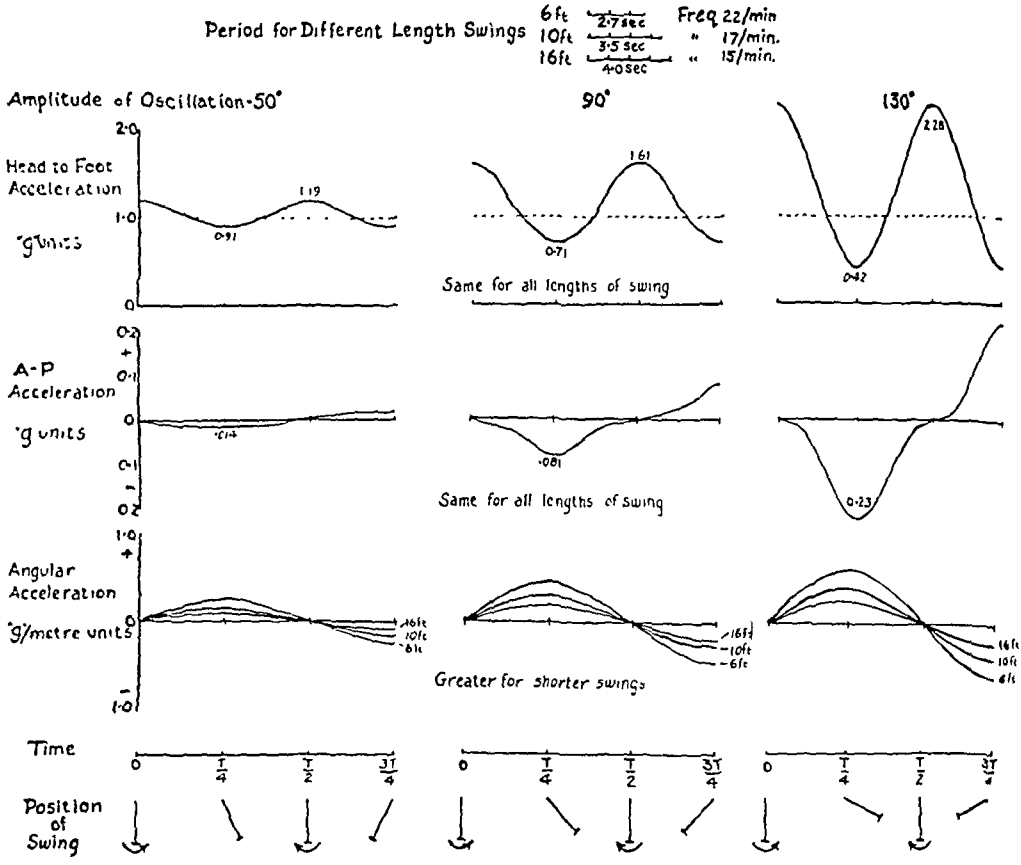

Fig. 2. CALCULATED FORCES (g units) for each type of swing used in these studies.

RESULTS

Table 1 summarizes data obtained in the series of tests designed to determine the effect of variation of the radius (that is, variation of frequency) upon the incidence of swing sickness.

Similarly table 2 summarizes data collected to demonstrate the effect of variation of the angle of oscillation (or quantity of g change) on incidence of swing sickness.

DISCUSSION

From table 1 it is apparent that when the angle is kept constant at 90 degrees, variation in the radius has a significant influence on incidence of swing sickness. The total incidence increased from 4 to 50 per cent on increasing the radius from 6 to 10 feet. However, on increasing the radius from 10 to 16

feet the total incidence only increased from 50 to 58 per cent, an insignificant increase. In seeking explanation for the low incidence on the 6-foot swing, several factors must be considered. First, of course, the frequency of oscillation is greater on the short swing. Secondly, although theoretically the components of acceleration and the resultant are the same on the 3 swings, the value of the resultant as measured was somewhat smaller on the 6-foot swing; further, the longer swings required a greater thrust (by hand) to maintain oscillation than did the short swing; the tangential component would be greater in the case of longer swings, and this might explain the slightly greater resultant g value obtained with the long swings, as compared with the 6-foot swing. It would seem possible, therefore, that differences in frequency of oscillation or of tangential acceleration or both might account for the observed differences in

TABLE 1. EFFECT OF FREQUENCY OF OSCILLATION ON INCIDENCE OF SWING SICKNESS

RADIUS OF SWING	ANGLE OF OSCILLATION	RANGE OF g CHANGE	MAXIMAL g CHANGE	COMPLETE OSCILLATIONS PER MINUTE ($2g$ CHANGES)	NUMBER OF MEN WITH EACH TYPE RESPONSE		
					I	II	III
feet							
6	90	0.7 –1.45	0.75	22	48(96%)	0	2(4%)
10	90	0.65–1.55	0.9	17	25(50%)	8(16%)	17(34%)
16	90	0.65–1.55	0.9	15	21(42%)	11(22%)	18(36%)

TABLE 2. EFFECT OF QUANTITY OF g CHANGE ON THE INCIDENCE OF SWING SICKNESS

ANGLE OF OSCILLATION	RADIUS OF SWING	RANGE OF g CHANGE	MAXIMAL g CHANGE	COMPLETE OSCILLATIONS/ MINUTE	NUMBER OF MEN WITH EACH TYPE OF RESPONSE		
					I	II	III
50	10	0.9 –1.15	0.25	17	39(78%)	5(10%)	6(12%)
90	10	0.65–1.55	0.9	17	25(50%)	8(16%)	17(34%)
130	10	0.4 –2.1	1.7	17	27(54%)	4(8%)	19(38%)

incidence of sickness. However, other work carried out simultaneously in this Unit (2) showed that subjects developed no sickness when placed on a vertical spring elevator, where the g changes were similar in frequency and quantity to those encountered on the 16-foot swing oscillating through 90 degrees. This suggests that the tangential component is important in the production of motion sickness, and that it may be responsible for the differences in incidence encountered using different radii. However, further work is required to determine whether this factor or the difference in frequency is the more significant in the results of table 1. Angular acceleration per se would appear to be of little importance. From table 1 it is apparent that the incidence of sickness decreased as the angular acceleration increased.

Table 2 shows that when the frequency is kept constant, increasing the amount of g change by increasing the angle of oscillation from 50 to 90 de-

grees, increased incidence from 22 to 50 per cent, whereas increasing the angle from 90 to 130 degrees had no significant effect. These results suggest a threshold mechanism, that is, increasing the g change within limits increases incidence of sickness, but increase of g beyond a moderate limit produces no further increase.

Calculations of the vertical tangential and angular forces developed on each of the swings used in the study are shown in figure 2. The measured forces are shown in figure 1. The tangential (A–P) forces were not measured, but from the calculated values it is apparent that these must be considered, for there is a significant increase from the 50-degree to the 90-degree swing, giving further evidence of the importance of the tangential component.

From other studies in which straight up and down motion or horizontal motion alone of similar magnitude does not produce motion sickness, it would appear that a threshold combination of at least 2 (or perhaps all 3) forms of motion is necessary for production of motion sickness.

SUMMARY

Human subjects were swung on a two-pole swing through angles of 50, 90 and 130 degrees, using radii of 6, 10 or 16 feet, to determine the importance of frequency and of quantity of g change in the occurrence of swing sickness.

The incidence of swing sickness was increased from 4 to 58 per cent when the frequency was decreased from 22 per minute on the 6-foot swing to 15 per minute on the 16-foot swing. Although theoretically the quantity of the forces acting remains constant when the angle remains constant, air resistance results in requiring a greater thrust to operate manually the longer swings; this would result in a greater tangential component of force, and the latter may be responsible for the increase in incidence as stated above. The low incidence of sickness on a vertical elevator, where there is no tangential component, supports this conclusion. The incidence of swing sickness was reduced from 50 to 22 per cent by reducing the oscillation angle from 90 to 50 degrees (or g change from 0.9 to 0.25). Increasing the angle from 90 to 130 degrees did not increase incidence of sickness. The frequency and quantity of g change on the 16-foot, 90-degree swing are similar to those of an elevator used in other work (2) in which sickness was almost absent. This suggests that the tangential component of force on the swing is necessary for production of sickness.

We wish to thank Dr. A. C. Burton, Professor of Biophysics, University of Western Ontario for figure 2 and the necessary calculations.

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Physiological Responses of Man to Inspiration of Hypoxic Oxygen-Nitrogen Mixture[1]

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THE PHYSIOLOGICAL RESPONSES to hypoxia have long been of interest both to the classical physiologist as well as to the student of cellular metabolism, and the tolerance to hypoxia has repeatedly emerged as a salient problem in the various aspects of applied physiology. The present study was initially undertaken during 1943 for the purpose of establishing control data of possible application in the then current search for objective measures of physiological response to various environmental stresses. This paper reports physiological findings obtained on a series of young men subjected to the stress of hypoxia by inhalation of an atmosphere of 9.5 per cent oxygen in nitrogen for a period of 20 minutes.

Among the measurable responses, five were selected and recorded, i.e., blood cell changes, arterial oxygen saturation, radial pulse rate, respiratory rate and ventilation volume. The first named has been previously reported (1), and the remaining four, along with the calculated tidal volume will be considered here. For these functions, the data have been disposed graphically to illustrate the time course of the observed responses and assayed statistically to furnish some estimate of the reliability of the measurements and the significance of their displacements.

PROCEDURE

The tests were conducted on a series of 26 volunteer naval personnel of ages between 18 and 30, and judged fit by prevailing medical standards. Each

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[1] The opinions expressed in this article are those of the author and do not necessarily represent those of the Navy Department or the Naval service at large.

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subject was required to breathe, in the sitting position, from an open spirometer system via face mask for *a*) a period of 5 minutes on room air, followed by *b*) 20 minutes on a 9.5 per cent O_2 in N_2 mixture and terminated with *c*) a 'recovery' period of 5 minutes, again on room air. A 120-liter spirometer was used for the periods on room air and one of 400-liter capacity for the hypoxic exposure interval.

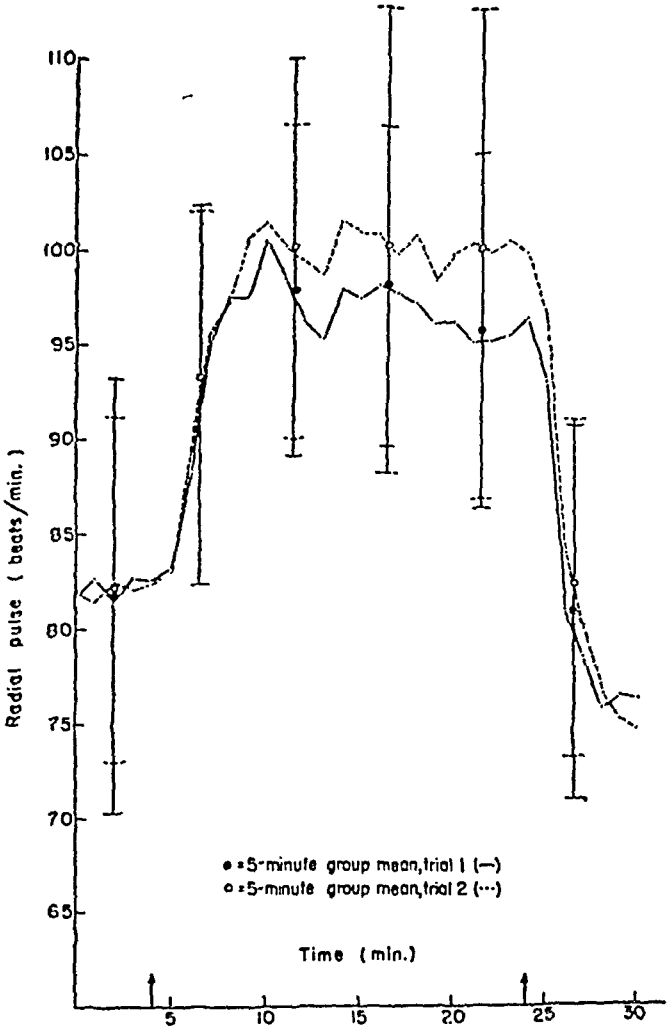

Fig. 1. PULSE RATE. *Arrows* indicate time course by minutes of average responses over hypoxic exposure period; *vertical bars* indicate $\pm \sigma$ from respective group means.

Two trials were conducted on each subject; the time interval between trials was about two months in one series (*series 1*, 12 subjects) and from 3 to 8 days in the remainder. Five of the latter group, however, have been dropped from the main comparisons since these were exposed for only 10 minutes to the low oxygen mixture. The number of subjects, then, becomes 21, and unless otherwise indicated the conclusions are based on this number.

After the subjects were seated and connected to the spirometers, minute readings for the 4 measures mentioned were obtained on each as follows: *a*) 20-second radial pulse count; *b*) 30-second count of respiration; *c*) 60-second interval reading of the spirometer to give ventilation volume; *d*) 60-second interval reading of the oximeter (Millikan type, Coleman modification) to give arterial oxygen saturation; *e*) respiratory tidal volume was computed from (*b*) and (*c*) after correcting (*c*) to STP dry; *f*) the blood samples were removed via anticubital venipuncture 5 minutes before starting time and during the last minute of the 20-minute exposure period. The specific time schedule of the measurements is available in a protocol format reported elsewhere (2).

RESULTS AND DISCUSSION

Graphic representation of the time course of the responses during the respective trials (figs. 1–5) was obtained by plotting the average minute values for all patients as a function of time. As is evident from the figures, the relative displacement in the various functional levels was greatest in the depression of the blood oxyhemoglobin and in the elevation of pulse rate. These changes amounted to about 30 and 20 per cent, respectively, of their pre-exposure levels and the mean differences were clearly significant ($P \leq .01$).

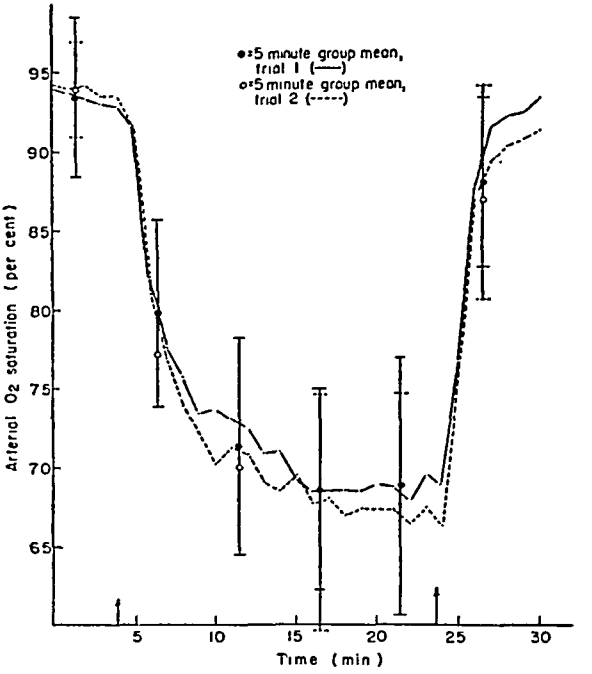

Fig. 2. OXIMETER READINGS. *Arrows* indicate time course by minutes of average responses over hypoxic exposure period: *vertical bars* indicate $\pm \sigma$ from respective group means.

The maximum displacement in the arterial pulse rate appeared to be attained after 5 to 10 minutes of the exposure and then to hold steady at around 100 beats per minute; the oxyhemoglobin level, however, appeared to reach its maximum depression a little later (i.e. after 10–15 minutes of exposure) and stabilized at a mean of 67 to 68 per cent saturation. It appears, therefore, that an hypoxic exposure period of about 10 minutes is all that is necessary to obtain maximum displacements of all functions measured.

Pulse rate was significantly correlated with the oxyhemoglobin saturation throughout the period of exposure

$$((t_{5-24})\ r_{xy} = -0.765 \pm 0.229)$$

and including the recovery period

$$((t_{5-30})\ r_{xy} = -0.929 \pm 0.200)$$

If the pulse rate were increased in response to the reduction in blood oxyhemoglobin concentration its compensatory value would depend largely upon the net change in cardiac output which may have resulted. In this respect the present data may be interpreted from some measurements by Starr and McMichael (3) taken on patients at 18,000 feet. These workers obtained data similar to those reported here and in addition estimated cardiac output from ballisto-cardiographic measurements. From the favorable comparison which obtains between the respective pulse rate, oximeter and respiratory data in

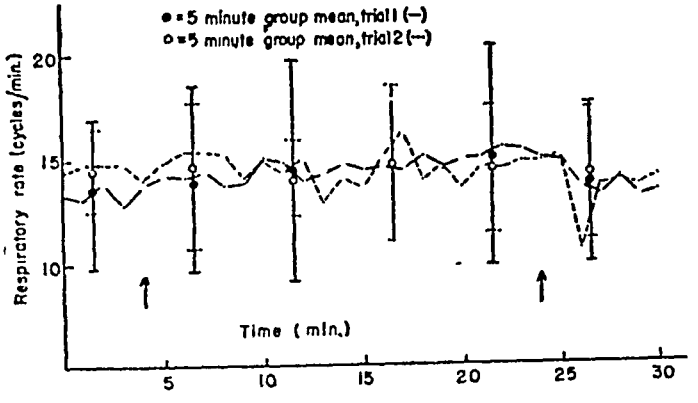

Fig. 3. RESPIRATORY RATE. *Arrows* indicate time course by minutes of average responses over hypoxic exposure period; *vertical bars* indicate $\pm\sigma$ from respective group means

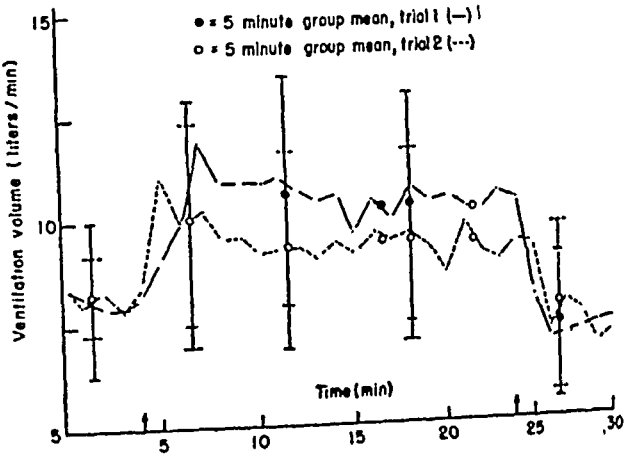

Fig. 4. MINUTE VENTILATION VOLUME. *Arrows* indicate time course by minutes of average responses over hypoxic exposure period; *vertical bars* indicate $\pm\ \sigma$ from respective group means.

the two studies it appears reasonable to infer that in our experiments also an increase in cardiac output occurred.

The respiratory response was highly variable throughout the trials. A 12 to 15 per cent increase occurred in the minute ventilation volume; this change was found to be significant in both trials. The respiratory rate showed greater variation about the means than did any other measures, but it increased slightly (8 per cent) in both trials, the change was significant in the first trial but not in the second. The theory of runs of Swed and Eisenhart (4) was used to test the significance of the respiratory data. The tidal volume is of course capable of treatment here only with reference to the two independent measures from which it was obtained and must therefore reflect the variance of both.

However, the mean values for respiratory rate appeared to be less affected by the exposure than was the minute volume (figs. 3, 4). The increase in minute volume was therefore primarily a function of increased tidal volume. In this

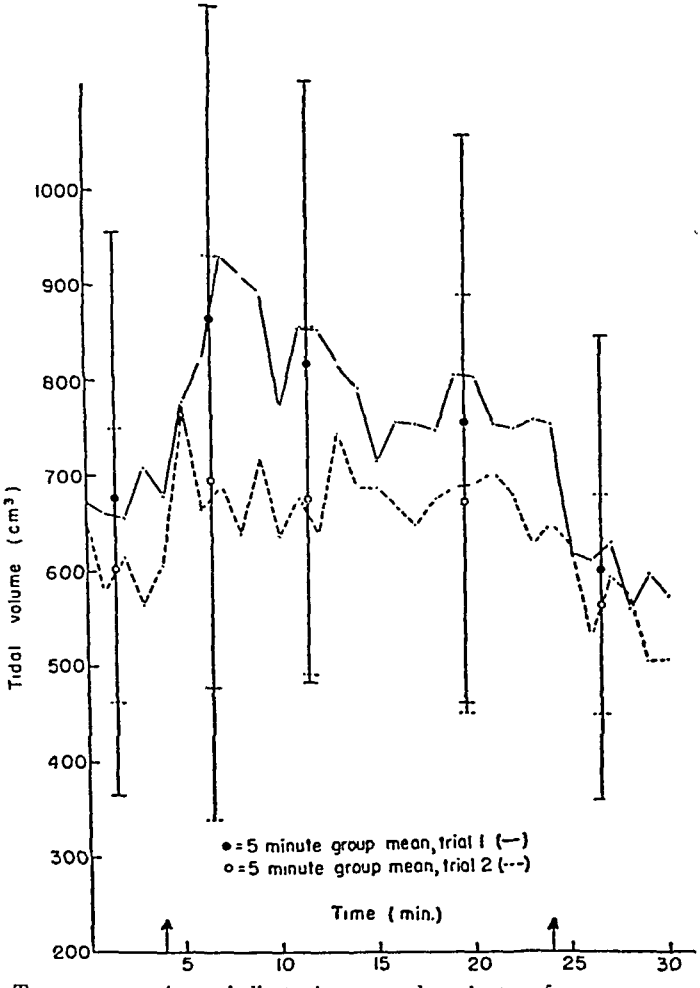

Fig. 5. TIDAL VOLUME. *Arrows* indicate time course by minutes of average responses over hypoxic exposure period; *vertical bars* indicate $\pm \sigma$ from respective group means.

regard, experiments in which the tidal volume was either measured directly, as with the Haldane concertina or was held constant, would be extremely pertinent.

A second objective of the studies reported here was to obtain, if possible, some measure of the predictability of the response to hypoxia in terms of the initial resting state. It was therefore undertaken to correlate the mean response during the initial 5-minute resting period with the means of succeeding inter-

vals of 5 minutes during the exposure period. The result of these correlations has been to indicate that no great predictability of the exposure response in terms of the initial level could be demonstrated for any of the 5 functions measured. Similarly the means of the initial 5 minutes of the exposure period proved unsatisfactory as a basis for predicting the response during subsequent periods of the exposure.

Again, correlations were obtained between the response during the first 5 minutes of exposure on the first trial and the response during a subsequent 5-minute period on the second trial. It was hoped by this means to obtain some added information as to the possible usefulness of the period of stress as a means of predicting the performance on a second occasion under the same stress. However, and as might have been predicted from the test-retest reliability assessments described herein, significant departures from zero were not obtained consistently in the coefficients for any of the functions.

A measure of the test-retest reliability of the various responses measured here was obtained by correlating the means of the first test for specific 5-minute intervals with those for the same 5-minute intervals on a second test. From this it was concluded that the reliabilities of all of these measures were too low to be ideal or even very useful as physiological criteria.

It should be noted that in several of the foregoing series of correlations significant values were obtained; however, there were sufficient inconsistencies in this respect to cast doubt upon the true validity of significance in these cases.

SUMMARY

Tests were made to determine the hypoxic effect of 9.5 per cent oxygen in nitrogen on human subjects. It was found that in response to the inhalation of this mixture during a period of 20 minutes, the pulse rate was significantly raised, i.e. by about 20 per cent of the resting value. Similarly the oxyhemoglobin saturation was observed to drop sharply with the beginning of the exposure period. Changes in the respiratory rate and the ventilation volume occurred; these were variable but appear to be significant.

It is concluded that the main compensation to the low oxygen exposure was made by the changes in cardiac output incident to the increased heart rate, and that increased ventilatory efficiency constituted a somewhat less important factor in this regard. An examination of the variance indicates that in general the functions tested do not constitute reliable criteria for physiological test use.

The author wishes to acknowledge the counsel of Dr. Nello Pace and the able assistance of Mr. C. J. Spear and other former members of the Physiology Facility, Naval Medical Research Institute.

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Mechanics of Breathing in Man[1]

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THE MECHANICAL WORK done by the respiratory muscles in producing the movements of breathing has been studied relatively little by physiologists. Although most text-books of physiology give values for the work done by the heart, similar estimates for the work of breathing are lacking. The classic contributions of Rohrer (1–3) lay the foundation for this subject, but only a few pertinent papers, notably those of Neergaard and Wirz (4), Vuilleumier (5), Bayliss and Robertson (6), and Dean and Visscher (7), have since appeared.

The material presented below, although based on data which are neither sufficiently precise nor extensive enough to furnish an exact description of the mechanics of breathing, constitutes an approximate analysis, which we have found valuable as a way of thinking about certain respiratory problems.

FORCES INVOLVED IN BREATHING

From the work of previous investigators and on the basis of *a priori* reasoning, we should expect that the respiratory muscles in carrying out the breathing movements would have to overcome several types of resisting forces. These forces will be mentioned briefly now and considered later in more detail. The chest and lungs are elastic in nature and must be stretched during inspiration to accommodate an increased volume. The air in moving through the respiratory tract encounters viscous and turbulent resistance, and there is probably some additional non-elastic resistance associated with deformation of tissues, and with the sliding of organs over one another when they are displaced. Finally, since the system is almost continuously accelerating or decelerating, inertia should be mentioned as a possible factor. The calculations of Rohrer (3), however, indicate that the force required for acceleration must be ordinarily very small, and we shall, in general, consider it negligible. Another factor of relatively inconsequential magnitude is the kinetic energy imparted to the air.

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[1] This work was completed under contract between the University of Rochester and the Air Materiel Command, Wright-Patterson Air Force Base, Dayton, Ohio. Some of our earlier work was reported in C.M.R. Report No. 430, May 10, 1945 and in *Federation Proc.* 6: 173, 1947. An abstract of a preliminary report, presented before the National Academy of Sciences, appears in *Science* 110: 443, 1949.

Elastic Forces. If a person relaxes his respiratory muscles completely, the lungs assume a volume close to that which is customary at the end of a normal expiration, the mid-capacity or *relaxation volume.* At this volume the elastic forces of the chest must be equal and opposite to those of the lung. When the chest-lung system is displaced to any other volume, elastic forces which oppose the displacing force are developed. The method of measuring these elastic forces as *relaxation pressures* and a curve showing the relationship between relaxation pressure and lung volume have been presented in a previous paper from this laboratory (8). The reciprocal slope, $\Delta P/\Delta V$, of the relaxation pressure curve is the elastic resistance or 'elastance' (pressure required to produce unit change in volume (6, 7)). Although the relaxation pressure curve is not linear, it is approximately so over a considerable part of its range, and as a first approximation the elastance may be expressed by the following equation:

$$P_{el} = KV \qquad (1)$$

where K is the elastance and P_{el} is the pressure developed when the displacement from the relaxation volume is V.

Air Viscance and Turbulence. A method for estimating the magnitude of the viscous and turbulent forces that must be overcome in moving air through the respiratory tract has been described previously (9, 10), and data have been presented which indicate that the relationship between these forces and the velocity of air flow may be described approximately by the following equation:

$$P_{alv} = k_1\left(\frac{dV}{dt}\right) + k_2\left(\frac{dV}{dt}\right)^2 \qquad (2)$$

where P_{alv} is the pressure gradient between alveoli and mouth that is required to move the air with a velocity (dV/dt). The constants k_1 and k_2 are the air *viscance*[2] and the *turbulent resistance*, respectively.

An example of the sort of record from which data were obtained for purposes of the present investigation is shown in figure 1, and the points obtained from measurement of records made on *subject R* are shown in figure 3. The parabola was fitted to these points by the method of residuals.

Resistance Associated with Tissue Deformation It does not seem feasible to measure directly the non-elastic resistance associated with tissue deformation, but an estimate may be obtained in the following fashion. A trained subject is placed in a Drinker respirator and is instructed to relax as completely as

[2] Our usage of the word 'viscance' in this paper is implicit in *equation 2* and may be used synonomously with 'viscous resistance', it is expressed in dimensions of pressure per unit flow of respired gas 'Viscance' was defined by Bayliss and Robertson (6) as "the viscous force per unit deformation" or "viscous pressure per unit of tidal air volume" Dean and Visscher (7), however, use the same term to mean "viscous resistance to a unit velocity of flow" Although the definition of Bayliss and Robertson was stated to make 'viscance' analagous to 'electrical resistance,' we believe that our usage of the term is a better analogy

possible so that his breathing movements are produced by the alternating pressure within the respirator instead of by the action of his respiratory muscles. The pressure gradient between the respirator and the mouth of the subject and the velocity of air flow are simultaneously recorded. The pressure recorded at any moment is, of course, that required to overcome the total resistance, and since the elastance and air viscance and turbulent resistance can be obtained as described above, the non-elastic tissue resistance can be estimated by difference. Figure 2 shows a sample record obtained in this type of experiment.

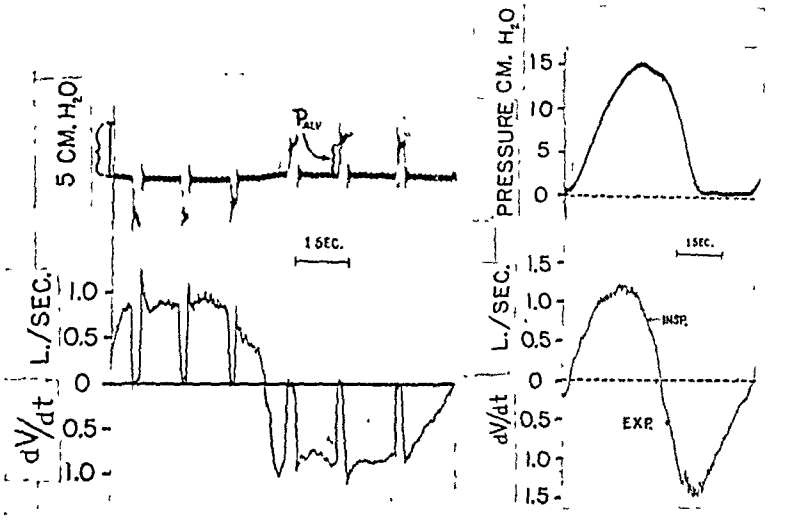

Fig. 1 (*left*). SIMULTANEOUS RECORDS of pressure at mouth (*upper tracing*) and pneumotachogram (*lower tracing*). In pneumotachogram, inspiration is above and expiration below baseline. Sudden changes in pressure at mouth and simultaneous interruptions of air flow were produced by brief closure of solenoid valve located in airway between mouth and pneumotachograph. Method of estimating alveolar pressure ($P_{alv.}$) is indicated.

Fig. 2 (*right*). SIMULTANEOUS RECORDS of pressure gradient between mouth and inside of Drinker respirator (*upper tracing*) and pneumotachogram (*lower tracing*). *Subject R.*

A useful way of representing some of the data that can be obtained from such a record is shown in figure 4 in which pressure is plotted against accumulated volume for one breathing cycle. The method of constructing such a diagram will now be described.

The velocity of flow and the simultaneous pressure were measured and tabulated for each 0.1-second interval of the record of the respiratory cycle shown in figure 3. Then starting at the beginning of inspiration each 0.1-second interval of the flow curve was integrated by multiplying the mean velocity of flow during each period by 0.1 second. This gave the volume that flowed during each 0.1-second period. These volumes were then added in a cumulative fashion and the total volume at the end of each time interval was plotted against the corresponding pressure gradient that existed at the end of

that interval. The plotted points determine the solid lines that form the large loop in figure 4.

This closed curve represents the relationship between the changes in the volume of the lung during the respiratory cycle and the external forces (as represented by the pressure gradient between the respirator and mouth) acting to produce this change. At two moments (when the cycle reverses from in-

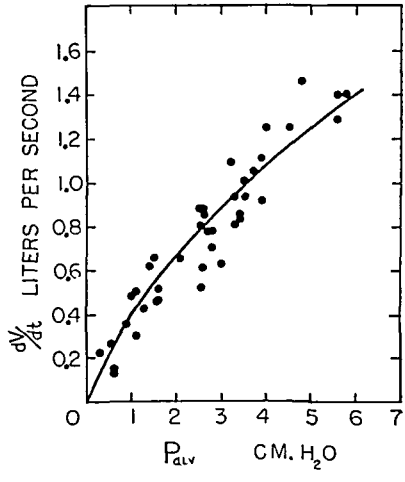

Fig 3 Relationship between instantaneous rate of flow of respired gas and pressure gradient between alveoli and mouth for *subject R* Curve drawn through points represents equation

$$P_{alv} = 1.7\left(\frac{dV}{dt}\right) + 1.9\left(\frac{dV}{dt}\right)^2.$$

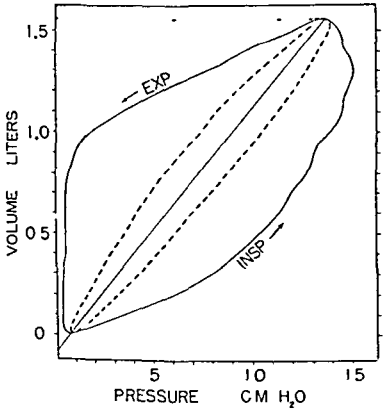

Fig 4 Relationship between volume of respired gas and pressure gradient during one respiratory cycle for *Subject R* For explanation, see text

spiration to expiration and vice versa) no air is being moved in either direction. At these instants, therefore, the total force acting is being used to maintain elastic tension that has been developed, inertia being assumed to be negligible. If we assume a linear relationship between elastic pressure and lung volume, then the diagonal in figure 4 represents this relationship. Approximately, it is a segment of the relaxation pressure curve.

Some of the information represented by figure 4 may be summarized as follows. As the lung volume is increased during inspiration, the total pressure

gradient between the mouth and the inside of the respirator is represented by the abscissal distance from the axis of ordinates to the inspiratory loop. Of this total inspiratory pressure ($P_{in.}$) at any given lung volume, a certain amount ($P_{el.}$), represented by the abscissal distance from the axis of ordinates to the diagonal, is required to overcome elastance; the remainder ($P_{in.} - P_{el.}$) is the pressure required to overcome air and tissue viscance and turbulent resistance.

Expiration is produced by the elastic forces that were developed in the chest and lung during inspiration. However, the total elastic force is not available, in this case, for overcoming the viscous and turbulent resistances of expiration, because the pressure within the respirator continues to be negative especially during the first part of expiration. The pressure actually used in overcoming viscance and turbulence at any moment during expiration is of course ($P_{el.} - P_{ex.}$) where $P_{ex.}$ is the abscissal distance from the axis of ordinates to the expiratory loop, i.e. the pressure gradient between the mouth and the inside of the respirator during expiration. Under the conditions of the particular experiment illustrated in figure 4, the lung volume does not quite get back to the relaxation volume by the end of expiration; the respirator starts an inspiratory movement before expiration is as complete as it would be if more time were allowed.

The relationship between numerous values of ($P_{in.} - P_{el.}$) or ($P_{el.} - P_{ex.}$) and the corresponding velocities of flow is represented by the points plotted in figure 5. These data were obtained from figures 2 and 4 and other similarly plotted cycles measured on *subject R*. The parabolic curve drawn through the point S was fitted by the method of residuals and may be generally represented by

$$P_n = K' \left(\frac{dV}{dt}\right) + K'' \left(\frac{dV}{dt}\right)^2 \qquad (3)$$

the slope of which represents the total viscous and turbulent resistance of breathing.

By subtracting the curve of figure 3 from that of figure 5 a relationship of the following form is obtained

$$P_t = k_3 \left(\frac{dV}{dt}\right) + k_4 \left(\frac{dV}{dt}\right)^2 \qquad (4)$$

Its slope represents the resistance associated with the non-elastic component of tissue deformation.

By means of *equation 4*, P_t was calculated for each 0.1-second interval of figure 2 and the resulting values were added to the corresponding values of $P_{el.}$ during inspiration and subtracted during expiration. These sums or differences were plotted against the cumulative volume for the corresponding time interval to form the loop indicated by the broken line in figure 4. The

abscissal distance from the diagonal to this loop is the pressure required to overcome non-elastic resistance of tissue.

Constants for *equations 1, 2, 3* and *4* evaluated as outlined above are recorded in table 1 for *subject R* and for two other subjects who were similarly studied. The values shown for each subject are based on measurements of several cycles.

Total Force Required for Breathing. The total force required for breathing is the sum of *equations 1* and *3* or

$$P_{\Sigma} = KV + K'\left(\frac{dV}{dt}\right) + K''\left(\frac{dV}{dt}\right)^2 \qquad (5)$$

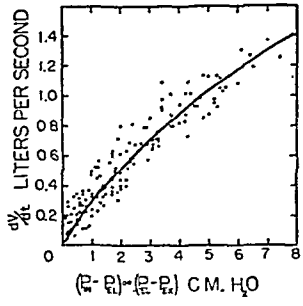

Fig. 5. Relationship between instantaneous rate of flow of respired gas and pressure required to overcome non-elastic resistance to breathing. *Subject R.* Curve drawn through points represents equation:

$$P_n = 2.7\left(\frac{dV}{dt}\right) + 2.1\left(\frac{dV}{dt}\right)^2.$$

Table 1. Values of resistance constants estimated for three subjects

Subject	Elastic resistance	Additional resistance of air		Additional resistance of tissue		Total additional resistance	
	K	k_1	k_2	k_3	k_4	K'	K''
	cm.H_2O/l.	cm.H_2O/(l/sec.)	cm.H_2O/(l/sec.)^2	cm.H_2O/(l/sec.)	cm.H_2O/(l/sec.)^2	cm.H_2O/(l/sec.)	cm.H_2O/(l/sec.)^2
R	8.00	1.7	1.9	1.0	0.2	2.7	2.1
B	9.38	3.2	0.8	1.0	0	4.2	0.8
D	8.19	2.9	1.4	0.6	0.1	3.5	1.5
Mean.....	8.52	2.6	1.4	.9	.1	3.5	1.5

THE WORK OF BREATHING

Another useful feature of the method shown in figure 4 of representing a breathing cycle is that area on such a diagram has the dimensions of work. For example, the area of the triangle formed by the diagonal, the horizontal broken line and the axis of ordinates in figure 4 represents the amount of work done during inspiration in overcoming elastic resistance. The area bounded by the diagonal and the curved line labeled *inspiration* is the additional work required to overcome the viscous and turbulent resistance of inspiration. This area may be subdivided into work done on non-elastic resistance of tissue (area between diagonal and broken line) and work done in overcoming air viscance and turbulent resistance.

The elastic energy stored during inspiration and represented by the triangle is available as a power supply for expiration. However, only that portion bounded by the diagonal and the curve labeled *expiration* is actually used in this instance to overcome viscous and turbulent forces; the remainder is expended in working against the continued action of the respirator which opposes expiration during the first part of this phase of the breathing cycle.

Table 2 summarizes measurements of the work of breathing and its fractions obtained by planimetric integration of diagrams such as that illustrated by figure 4. These data indicate that on the average 63 per cent of the total work done in inspiration was used in overcoming elastic forces, 29 per cent in

TABLE 2. WORK OF BREATHING IN DRINKER RESPIRATOR AT FREQUENCY OF 15 PER MINUTE

SUBJECT	TIDAL VOLUME	TOTAL WORK OF INSPIRATION	ELASTIC WORK OF INSPIRATION	WORK ON AIR DURING INSPIRATION	WORK ON TISSUES DURING INSPIRATION
	*cm.*³	*gm. cm.*	*% of total*	*% of total*	*% of total*
R	1550	17,295	63.0	27.4	9.5
	1340	13,170	59.7	31.5	8.8
	950	6,265	61.5	27.8	10.7
	500	2,091	63.6	28.8	7.6
B	2275	47,660	66.8	25.8	7.4
	1620	23,665	69.2	22.7	8.1
	840	6,220	60.1	32.1	7.8
D	995	7,462	59.6	34.9	5.5
	1365	9,225	65.8	25.0	9.2
	1095	7,720	64.0	28.7	7.3
Mean Values.....			63.3	28.5	8.2

overcoming resistance associated with the movement of air, and 8 per cent in deforming tissues. These percentages apply, of course, only to the particular pattern of breathing employed in this experiment. As will be pointed out later, both the absolute and relative magnitudes of these factors depend to some extent on the particular pattern of breathing employed.

If one assumes that *equation 5* is reasonably valid, the information contained in it makes possible the estimation of the work of breathing for any breathing cycle for which the velocity pattern (pneumotachogram) is known. One method would be to calculate the corresponding pressures for numerous points along the velocity curve and then to follow the procedure described above that was used in getting the data of table 2. This empirical method is very tedious, however, and if one can describe the velocity curve by a simple mathematical expression, the work of breathing may be calculated in a more direct fashion.

For example, assume as a first approximation that the velocity pattern of inspiration is a sine wave (fig. 6). Then

$$\frac{dV}{dt} = a \sin bt \tag{6}$$

where dV/dt is the velocity of air flow, a is the maximal velocity, and $b/2\pi = f$ is the frequency of breathing.

The tidal volume, V_T, is given by

$$V_T = \int_0^{\pi/b} a \sin bt\, dt = \frac{2a}{b} = \frac{a}{\pi f} \tag{7}$$

The differential expression for work is $dW = PdV$ which by substitution from *equations 5* and *6* becomes

$$dW = KV\, dV + K'a^2 \sin^2 bt\, dt + K''a^3 \sin^3 bt\, dt \tag{8}$$

In this expression for the differential of work, the first term represents elastic work, the second viscous work, and the third work done in overcoming

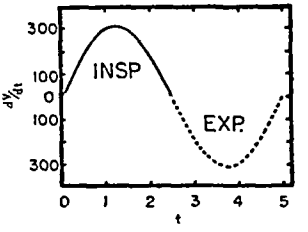

Fig. 6. IDEALIZED REPRESENTATION of pneumotachogram as sine wave. *Ordinates:* Flow of respired gas in cc/sec. *Abscissae:* Time in sec. In this example a mean ventilation of 6 l/min. with tidals of 500 cc. and frequency of 12 breaths/min. is assumed. Constants of *equation 6* in this case are, therefore: $a = 314$ cc/sec. and $b = 0.4\,\pi$ reciprocal seconds.

turbulent resistance. The total work done during a single inspiration of volume V_T and duration π/b may be obtained by integration of *equation 8* as indicated below

$$W = \int_0^{V_T} KV\, dV + \int_0^{\pi/b} (K'a^2 \sin^2 bt + K''a^3 \sin^3 bt)\, dt \tag{9}$$

$$W = \tfrac{1}{2}KV_T^2 + \tfrac{1}{4}K'\pi^2 f V_T^2 + \tfrac{2}{3}K''\pi^2 f^2 V_T^3 \tag{10}$$

The mean rate of doing work is the work per breath times the frequency of breathing.

Mean rate of work =

$$\tfrac{1}{2}Kf V_T^2 + \tfrac{1}{4}K'\pi^2(f V_T)^2 + \tfrac{2}{3}K''\pi^2(f V_T)^3 \tag{11}$$

This is the inspiratory work per unit time but if it is assumed that expiration is passive, it is of course an expression of the total work of breathing per unit time as a function of tidal volume and frequency. If the tidal volume is divided into an effective or alveolar portion, V_A, and a dead space portion, V_D, *equation 11* becomes

Work per unit time =

$$\tfrac{1}{2}Kf\left(\frac{\dot{V}_A}{f} + V_D\right)^2 + \tfrac{1}{4}K'\pi^2(\dot{V}_A + fV_D)^2 + \tfrac{2}{3}K''\pi^2(\dot{V}_A + fV_D)^3 \qquad (12)$$

where $V_A f = \dot{V}_A$ = alveolar ventilation.

By *equation 12* the rate of work of breathing can be calculated for any given alveolar ventilation, frequency and dead space. Figure 7 shows the calculated work per minute at various breathing frequencies when the alveolar ventilation is 6 liters per minute and the dead space is assumed to be constant at 200 cc., values which are reasonably typical for a resting subject.

In making these calculations the mean values for K, K' and K'' given in table 1 were converted to appropriate units so that $\dot{V}_A$ could be expressed in liters per minute and f in breaths per minute and rounded off for ease of computation. The equation as used was gm. cm. of work per minute =

$$5000f\left(\frac{\dot{V}_A}{f} + 0.2\right)^2 + 150(\dot{V}_A + 0.2f)^2 + 3(\dot{V}_A + 0.2f)^3 \qquad (13)$$

Of special interest is the fact, illustrated by this graph, that for a constant alveolar ventilation there is a frequency which is optimal (in the sense of minimal work). This minimum occurs because when the frequency is too low, much elastic work is required to produce the large tidal volumes and when the frequency is too high, much work is uselessly done in ventilating the dead space with each breath.

The fact that the optimal frequency in this case is in the range ordinarily observed in the breathing of resting subjects suggests itself as an example of the principle of minimal effort according to which so many of the body functions seem to be regulated.

By differentiating *equation 12* with respect to f, setting the result equal to 0, and solving for V_A we have the general solution for the conditions of minimal rate of doing work.

$$V_A = \frac{KDf + K'\pi^2Df^2 + 4K''\pi^2D^2f^3}{K - 4K''\pi^2Df^2} \qquad (14)$$

Various values of f have been substituted in *equation 14* and the resulting curve is shown in figure 8 (curve labeled $W_{min.}$). This curve predicts that the greater the alveolar ventilation, the higher will be the frequency for the condition of minimal work. Since this curve actually applies to the condition of minimal inspiratory work, it can not be accepted for minimal total work unless expiration is completely passive. The curve labeled $W_V + W_T = W_E$ in figure 8 shows the frequency at which the work required for expiration (assuming this is the same as that required to overcome viscous and turbulent resistance of inspiration) becomes equal to the elastic energy stored during inspiration. Conditions represented by the area above this curve will, therefore, require the

active participation of the expiratory muscles. For alveolar ventilations greater than about 15 liters per minute, the curve $W_{min.}$, while defining conditions for minimal inspiratory work, will predict frequencies that are too high for minimal work of inspiration plus expiration. The curve $W_V + W_T = W_E$ defines, in a sense, conditions for minimal expiratory work in that it indicates conditions such that the elastic energy stored in inspiration is just enough to meet the needs of expiration. At the higher alveolar ventilations, however, the conditions demanded by this curve become absurd, because the required tidal volume becomes impossibly large. The conditions for a tidal volume of 4 liters are indicated for purposes of illustration, by the line $V_T = 4$.

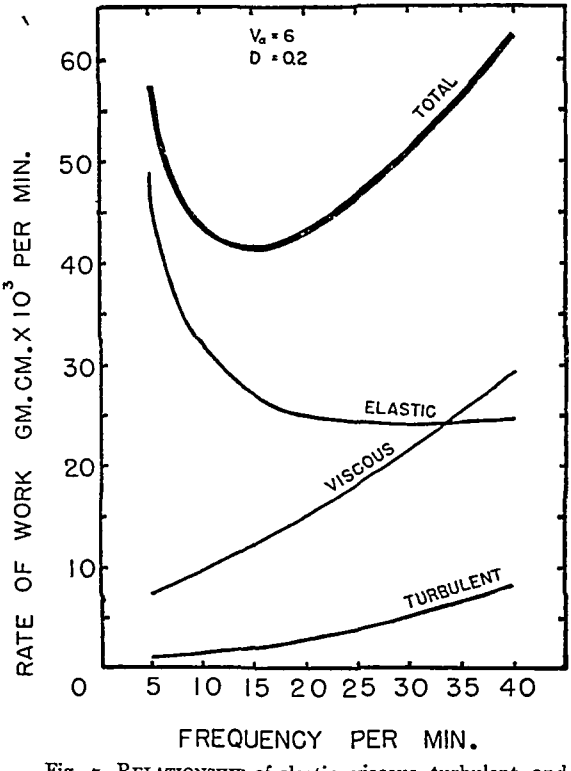

Fig. 7. RELATIONSHIP of elastic, viscous, turbulent, and total work of breathing/min. to frequency of breathing when alveolar ventilation is 6 l/min., and dead space is 200 cc. Curves calculated according to *equation 13*.

One might expect then that for the lower range of ventilations the optimal frequency would be defined by curve $W_{min.}$, but at the higher ventilations the optimal frequencies would lie between the curve $W_V + W_T = W_E$ and the dotted section of curve $W_{min.}$

Several sets of data from the literature showing frequencies voluntarily chosen by subjects whose breathing was stimulated by added dead space, by CO_2 added to the inspired air, or by exercise bear out this expectation in a general way, as indicated by the plotted points in figure 8.

Although these considerations yield no exact description they do perhaps indicate roughly how various factors may interact to determine the frequency at which we breathe under various ventilatory requirements. It would be desirable, of course, to determine what the exact velocity patterns of inspiration and of expiration should be for optimal conditions. To do this would require a much more involved treatment which is probably not justified without more exact data as a basis.

The above discussion has been predicated on the principle of minimal effort but we do not wish to imply that this is the only principle involved. Another important consideration, especially in unusual situations, might be called the 'principle of maximal comfort.' If a patient with pleurisy, for example, finds that one pattern of breathing is less painful than another, it is likely that he will sacrifice a few calories for the sake of comfort.

Mechanical Efficiency of Breathing. Several investigators (11–13) have estimated the total energy required for breathing at various depths and frequencies by measuring the extra oxygen consumption during hyperpnea either voluntarily produced or stimulated by CO_2 added to the inspired air. The most comprehensive series of such measurements is that of Liljestrand (11), whose data are represented in part by the solid lines in figure 9.

On the same graph are plotted dotted lines representing the mechanical work (calculated by *equation 11*) required for the corresponding conditions of

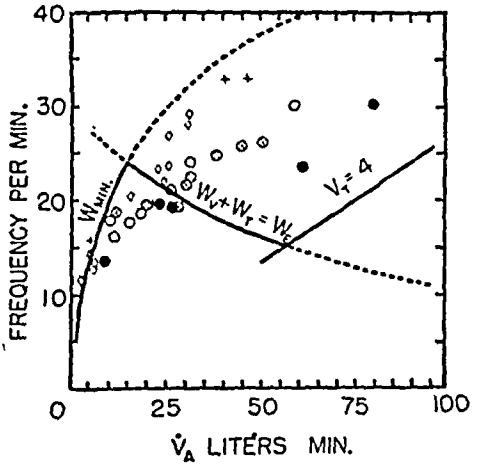

Fig. 8. FACTORS DETERMINING OPTIMAL BREATHING FREQUENCIES for various alveolar ventilations. For explanation of curves, see text. Plotted points represent data from literature as follows: *open circles, subject R.M.*, Barcroft and Margaria (21); *solid circles, subject J.B.*, Barcroft and Margaria (21); *circles with X, subject J.J.*, Lindhard (22); *diamonds, subject I.B.*, Hansen (23); *crosses, subject G.L.*, Liljestrand (11). Alveolar ventilations calculated from recorded total ventilations by assuming dead space of 200 cc.

ventilation and frequency. The scale of ordinates for the calculated mechanical work has been adjusted so that it is equal to 5.4 per cent of that for the extra oxygen consumption. This figure is the average of 19 values obtained by dividing each of Liljestrand's measurements into the mechanical work calculated for the corresponding condition. The individual values for mechanical efficiency obtained in this fashion varied from 3.0 per cent for a frequency of 5 and a ventilation of 20 liters per minute to 7.6 per cent for a frequency of 20 and a ventilation of 30 liters per minute.

This variation in the calculated efficiency is reflected, of course, in the discrepancies between the curves for total energy and those for mechanical work in figure 9, because exact agreement between these two families of curves would require that the calculated efficiency be constant for all conditions.

Part of this apparent variability in efficiency under different conditions can, of course, be attributed to the inexactness of our equation for calculating

mechanical work, but part is probably real, since it is well known that the efficiency of muscular work varies with muscle length and load.

In Liljestrand's experiments the breathing was voluntarily regulated and for the most part the tidal-frequency combinations employed were not those that the body naturally chooses (cf. figs. 8 and 9). It is perhaps of significance that the highest calculated efficiency appears for the condition (30 l/min. at a frequency of 20) that most closely corresponds to a naturally occurring one. This suggests that the respiratory apparatus may be so designed that the

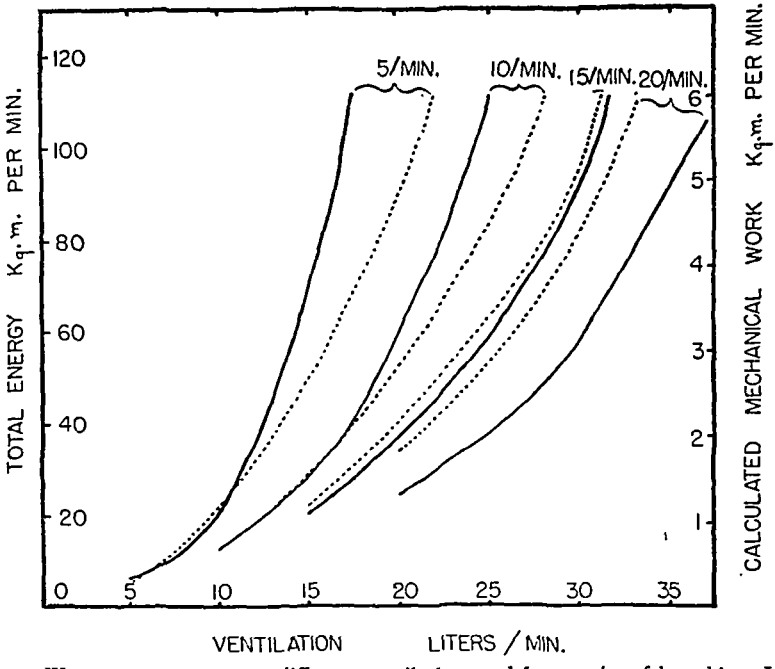

Fig. 9. WORK OF BREATHING at different ventilations and frequencies of breathing. *Left-hand scale of ordinates* refers to solid lines which represent total energy turnover as obtained by conversion of Liljestrand's (11) data for extra oxygen consumption. *Right-hand scale* refers to dotted lines which represent mechanical work calculated from *equation 11*.

conditions for minimal mechanical work are also those for maximal muscular efficiency.

At any rate it would seem that although 5 per cent is a representative efficiency for a considerable range of frequency-tidal combinations, the breathing under normal conditions of regulation may be usually carried out with a higher efficiency, in the order of 8 to 10 per cent.

It might be supposed that the relatively low mechanical efficiency of respiration could be attributed to insufficient opportunity for shortening of the intercostal muscles. Since they are arranged parallel to the circumference of the chest it might be supposed that they would have difficulty in shortening

when the chest expands. Actually they are attached to the ribs in such a way that they can shorten an appreciable fraction of their length like any other muscles in the body. It is a general rule that muscles can shorten *in situ* only 50 per cent of the length of the individual fibers and the muscles of respiration are no exception in this respect. Isolated frog muscles, when stimulated, usually shorten, with no load, about one third of their resting length, and give maximal work and maximal efficiency when the load is such as to reduce this shortening to about one sixth. From this point of view, the muscles of respiration must operate under fairly efficient mechanical circumstances.

Maximal Work Obtainable from the Muscles of Breathing. The mechanical work done in the usual resting breathing may be estimated from figure 7 as being in the order of 0.4 to 0.5 kilogram meters per minute. Assuming an efficiency of 5 per cent this corresponds to a total energy requirement of about 0.0234 large calories per minute or 33.7 large calories per day. This amounts to only 1 or 2 per cent of the total resting metabolism; the fuel requirement for 24 hours of quiet breathing is only 10 grams of sugar, a fraction of a candy bar.

For comparison, it is interesting to estimate the maximal work output that can be obtained when the breathing system is operated at full capacity. This estimate may be made by three independent methods, which will now be described.

The maximal ventilation that an individual can perform is in the order of 150 liters per minute carried out at a frequency of 30 per minute. Under these conditions expiration can not be entirely passive, but if one assumes that the same amount of viscous and turbulent resistance must be overcome during expiration as during inspiration, and that the elastic energy stored during inspiration is available to aid expiration then inspiratory work rate can be calculated by *equation 11* and expiratory work rate by:

Rate of expiratory work =

$$\tfrac{1}{4}K'\pi^2(fV_T)^2 + \tfrac{2}{3}K''\pi^2(fV_T)^3 - \tfrac{1}{2}KfV_T^2 \qquad (15)$$

The total work per unit time is the sum of *equations 11* and *15*, or

Work rate =

$$\tfrac{1}{2}K'\pi^2(fV_T)^2 + \tfrac{4}{3}K''\pi^2(fV_T)^3 \qquad (16)$$

By *equation 16* it is calculated that the mechanical work required for maximal ventilation is 270 kilogram meters per minute or 9.0 kilogram meters per breath.

Another approach is to estimate the potential energy available for maximal inspiration and expiration from figure 1 of Rahn, Otis, Chadwick and Fenn (8) which shows the maximal inspiratory and expiratory forces available at various lung volumes. The total area bounded by the curves for these maximal forces gives the theoretical maximal work available during a single cycle con-

sisting of a maximal inspiration and expiration. This method yields an estimate of 10 4 kilogram meters.

The maximal muscular forces available may also be estimated from anatomical data relating to the length, cross sectional area, and degree of shortening of the respiratory muscles. According to von Ebener (14) the lengths of the external and internal intercostals are 1.3 cm. and 1.6 cm. respectively, and in a full inflation or deflation of the chest the degree of shortening is about one eighth to one fourth of the muscle length for the former and one third to one half for the latter. The total cross sectional area of all the internal intercostals on one side of the chest is given by Weber, cited from Strasser (15, p. 143) as 97 $cm.^2$, and the corresponding figure for the external intercostals is 47 cm^2. Taking the force of contraction of these muscles as being similar to that for other human muscles (about 10 kg/cm^2 cross section) we have calculated the maximal work and entered the value in table 3, where the estimates by the other two methods are shown for comparison.

The value from the area of the *P-V* diagram is probably the most reliable

TABLE 3 MAXIMAL WORK AVAILABLE FOR BREATHING

METHOD OF ESTIMATION	WORK/BREATH	WORK/MIN AT 30 BREATHS/MIN
	kg m	*kg m*
Equation 16	9 0	270
Area of P-V diagram	10.4	312
Anatomical data	8 0 — 13 5	240 — 405

since it is based on actual measurements on 15 individuals. The estimate by *equation 16* is of course a large extrapolation from rather scanty data and involves numerous assumptions. The calculation from the anatomical data must also be considered as only approximate. The work of the diaphragm is omitted from this calculation because we do not have the necessary data.

Considering the admittedly rough methods involved, the similarity of these values is quite gratifying and gives one confidence that the estimates are at least of the correct order of magnitude.

It is interesting to note that although the maximal ventilation is only about 15 to 20 times the resting ventilation, the rate of work required is about 500 times greater for the former. Of course, this maximal work output can be kept up for only short periods of time, but the margin of safety provided for emergencies is impressively large.

COMMENT

The above presentation should be regarded as only an approximate overall picture of the respiratory apparatus considered from the mechanical point

of view along the lines sketched by Rohrer (3). Experimentally, the most inexactly estimated factor is probably the value for the non-elastic resistance of tissue since this determination was based on the assumption that the subjects were able voluntarily to relax completely and to permit the respirator to do all the work. Complete passivity is most likely not attained under these conditions, and the overlapping of the two sets of data shown in figures 3 and 5 is probably in part a manifestation of this inability to relax completely. Wirz (16) was able to describe the non-elastic resistance of the dog lung by an equation of the same form as our *equation 4* but he obtained negative values for the constant k_4. According to Bayliss and Robertson (6) and Dean and Visscher (7) at least a part of the non-elastic resistance of the lung is independent of velocity. For these various reasons we do not have confidence in the actual values obtained in our evaluation of non-elastic resistance of tissue. It seems likely, however, that we may have overestimated rather than underestimated the magnitude of this factor.

The approach employed in this analysis of the work of breathing, with emphasis on energy relationships and efficiency, is not to be justified so much by the importance of the magnitude of the work, which is generally relatively small, but rather as an aid in clarifying the interrelationship of some of the various factors involved.

In a more detailed analysis many factors would have to be included that are here omitted. For example, there is now good evidence that ventilation to various parts of the lungs is unequal (17, 18). It is also recognized that for optimal conditions of gas exchange a certain relationship should be maintained between blood flow and ventilation (19, 20). Since the breathing apparatus is a blood pump as well as an air pump, it may play an important part in the regulation of this ventilation/blood flow ratio. Certain patterns of breathing may be more efficient than others in this regard, and the selection by the body of particular tidal-frequency combinations may be related to this function.

Further study of respiratory mechanics should include investigation of the more detailed behavior of the respiratory muscles, their sequence of contraction and the behavior of the lungs in producing inequalities of ventilation. The work done by the breathing apparatus in moving blood as well as air should be evaluated, and the relationship between the pattern of air flow and that of blood flow should be considered.

SUMMARY

Relaxed human subjects were ventilated by a Drinker respirator while the velocity of respired gas flow and the pressure gradient between the mouth of the subject and the inside of the respirator were continuously and simultaneously recorded. From such experiments elastic resistance and total resistance to breathing were estimated. Resistance related to moving gas through

the respiratory tract was measured on the same subjects by the method of interruptions. From the experimental data equations are derived that give an approximate description of the human breathing apparatus as a mechanical system. These equations permit the estimation of the work of breathing under various conditions, optimal frequencies of breathing, maximal mechanical work output of the respiratory muscles, and mechanical efficiency.

The authors wish to acknowledge the cooperation of Dr. Donald Proctor in some of the preliminary experiments and to thank Mr. William Doherty for technical assistance.

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Individual Differences in Vascular Responses and Their Relationship to Cold Tolerance[1,2]

MORTIMER E. BADER[3] AND JERE MEAD,[4] with the technical assistance of M. ELIZABETH PILLION. *From the Department of the Army, Quartermaster Climatic Research Laboratory, Lawrence, Massachusetts*

THAT INDIVIDUALS VARY markedly in their ability to perform under cold stress is well known. Some men seem to be particularly resistant to frostbite, can work with unprotected hands for considerable periods in the cold, or withstand relatively long exposure under generalized cold stress without complaint. Others may be incapacitated under the same circumstances. It is apparent that these individual differences must relate to a large number of factors. Experience, training, attitude toward the cold and out-of-door life, mechanical ability and general coordination, intelligence, body build and fat distribution all play a part. In addition, there may be significant individual differences in the specific physiological responses of the body to cold which would markedly influence cold tolerance.

This study attempts to evaluate the extent to which demonstrable differences among individuals in physiological responses, similar to those that take place under cold stress, correlate with the abilities of these individuals to perform in the cold. This work was carried out at Fort Churchill, Manitoba, Canada, during the winter of 1948-49.

A variety of vascular responses, particularly of the fingers, was studied in 24 men and compared with an evaluation of their general and local tolerance to cold. These subjects ranged in age from 18 to 45 years, including 11 Americans (*B, E, H, I, J, K, L, O, S, T, U*), 10 Canadians (*C, D, F, G, N, Q, R, V, W, X*) and 3 British Subjects (*A, M, P*).

The subjects were evaluated from the standpoint of their ability to with-

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[1] This work has been performed in collaboration with the Medical Department, U. S. Army, which has assigned Medical Corps Officers to the Quartermaster Climatic Research Laboratory for research on adaptations of man to environmental stress.

[2] For material supplementary to this article, consisting of 8 pages of Appendix with 3 tables and 6 figures, order Document 2832 from American Documentation Institute, 1719 N Street, N.W., Washington 6, D. C., remitting $0.50 for microfilm (images 1 inch high on standard 35 mm. motion picture film) or $0.50 for photocopies (6 x 8 inches) readable without optical aid.

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stand cold both generally and locally (retention of manual dexterity or ability to manage well with minimal hand protection). Subjective reactions were collected on a questionnaire which was designed to determine the extent of Arctic experience, susceptibility to frostbite as well as the part or parts most frequently involved, and the individual's own estimate of his ability in the cold. Further data were collected from colleagues and superior officers of the subjects.

INSTRUMENTATION

A constant temperature chamber was utilized for all of the physiological studies. Ambient temperature was maintained at 90°F.±2°F. through the course of the experiments. Relative humidity varied between 15 and 30 per cent.

Finger Plethysmography. A Burch-Winsor finger plethysmograph (Cambridge Instrument Company) was utilized (1). Five cu. cm. of the terminal phalanx of the third finger of the right hand were inclosed in the plethysmograph cup. The cups were individually fitted to minimize compression of tissue and were sealed with printer's roller compound. The plethysmograph's sensitivity was adjusted so that a 10-mm. deviation on the record represented a 10-cu. mm. volume change of the 5-cc. segment of finger. The finger was immobilized on an air-evacuated rubber sand bag at heart level.

Blood Pressure Recording. A sphygmotonograph (Cambridge Instrument Company) was utilized for blood pressure determination in the left arm (2). A double inflatable cuff was wrapped around the upper arm. The pressure within the cuff, which was recorded on a chart, intermittently adjusted either to the systolic or the diastolic pressure, as determined by a control on the instrument. When operated in the diastolic position, a determination was recorded approximately every 5 seconds. In the systolic position, the determinations were somewhat more frequent. Systolic and diastolic pressures were obtained in the same arm by auscultation before and after each run.

Respiration Recording. A plastic capsule with a thin rubber diaphragm was mounted on the plethysmograph so that the shadow of the diaphragm fell on an edge of the camera slit. This capsule was connected by rubber tube to a narrow inflated tube surrounding the test subject's chest.

Foot Immersion Bath. A snow water bath was utilized. Immersion was accomplished by raising the bath from the floor by means of a simple pulley system, so that the feet were surrounded by water at 32°F.±1°F. to the level of the malleoli. Following immersion, the feet were first warmed by means of warm wet towels and then dried.

PROCEDURE

The subject, wearing shorts, entered the constant temperature room where he remained for at least one hour prior to the actual test. He was then seated

comfortably in an arm chair with all the apparatus properly applied and, for 5 minutes, control measurements of his pulse amplitude and finger volume were recorded. The subject was then instructed to take a deep breath, and this stimulus was repeated several times. A problem in mental arithmetic was then presented to the subject, e.g. multiply 16×17. The time of solution, if any was arrived at, was recorded. During the course of the test procedure, at a time when the subject was unaware of any impending stimulus, one of the observers would abruptly voice a loud yell, which served as a very satisfactory startle stimulus. A pain stimulus consisting of pulling a hair from the leg of the subject without warning was also applied. Cold immersion of the feet was produced on 4 occasions during the procedure.

Prior to each of these, control values were recorded both on the plethysmograph and blood pressure apparatus. A 30-second warning was given prior to immersion. The feet were then immersed above the ankles for one minute. The time of onset and severity of pain (if any were felt) were recorded. The interval between immersions was approximately 5 minutes. During the first two immersions diastolic blood pressures were recorded, and during the last two, systolic pressures. An attempt was made during the whole procedure to minimize extraneous psychological stimuli. In all subjects studied, at least 4 cold immersions (of the feet) were performed, and in the 14 on whom a repeat study was done, 8 observations were made.

A test of hand cold tolerance was performed on 6 of the subjects, *B*, *E*, *H*, *I*, *K*, *U*, at Lawrence, Massachusetts, approximately 3 months after the other studies. Subjects, similarly clothed, sat in a constant temperature room at 85°F. in ordinary clothing for one hour prior to the test. The subjects then entered a cold room (−10°F.) and sat quietly with the palms of their hands resting on the edge of a wooden table and their fingers extended. At one-minute intervals they untied a square knot tied with uniform tension by the test observer. The time at which the subjects were no longer able to perform this task was recorded. In every instance the limiting factor was intense pain sensation in the fingers. Each subject was tested on two separate days.

METHODS OF INTERPRETATION OF RECORDS

Interpretation of the Plethysmograph Tracing. The chief index of the state of digital blood flow utilized was the volume of pulsations in cu. mm/5 cc. tissue. Changes in mean finger volume were also measured.

Digital pulse volume and digital mean volume determinations afford a continuous record of events, which, in terms of roughly quantitative alterations in blood flow rates, is easy to interpret (4, 5). A decrease in pulse volume or mean finger volume indicates a decrease in the rate of blood flow through the part, and an increase in pulse volume or mean volume, an increase in the rate of blood flow through the part. In expressing pulse volume changes, a

ratio of the control values to the observed values, which expresses the relative rather than the absolute magnitude of change, has been utilized. This method of expression was employed because it is relatively independent of the volume of the part studied, and hence, of the errors inherent in the technique utilized for measuring the absolute volume of the part. Furthermore, this method gave more consistent results in an individual, and in differences between individuals, than did figures for absolute pulse volume changes. As recorded in this report, a ratio of 1.0 indicates no change; 2.0, a 50 per cent reduction in pulse volume; 3.0, 66.7 per cent reduction, etc.

The following measurements of spontaneous variations were recorded from each plethysmographic tracing: *a*) The maximal, minimal and average pulse volume of each individual occurring during the 5-minute control run; and *b*) an evaluation of spontaneous mean volume changes (so-called 'alpha waves' (1)) during the control period in which 3 types were recognized: *Class I.* Tracings with alpha wave amplitudes of 15 cu. mm. or less. *Class II.* Tracings with alpha wave amplitudes between 15 and 45 cu. mm. *Class III.* Tracings with alpha wave amplitudes greater than 45 cu. mm.

No attempt was made to measure the frequency or amplitude distribution of these spontaneous waves because of the extreme minute-to-minute variation even within a single individual, which rendered the 5-minute tracing inadequate for this purpose. The respiratory tracing permitted consideration of spontaneous waves independent of the variations occurring with respirations.

Measurement of Variations Occurring Following Specific Stimuli. The time of onset, volume change, pulse volume change, and duration of response occurring after the following stimuli were recorded: *1*) deep respiration; *2*) a loud yell given without warning; *3*) an attempt at solving a problem in mental arithmetic; *4*) pulling a hair without warning; *5*) warning 30 seconds prior to foot immersion; *6*) immersion of feet in ice water.

Although each of these stimuli is categorized as a single stimulus, it is in reality a complex stimulus, since each is markedly conditioned by psychological factors. Cold immersion was most complex in this regard; apprehension, startle, intense cold sensation, and pain in varying degree were all present.

Interpretation of Blood Pressure Responses. Blood pressures before and after each run were obtained by auscultation. Blood pressure changes occurring during cold immersion are expressed in mm. Hg and represent the maximal deviation from control levels occurring at any time during immersion.

Time onset of pain during cold immersion was recorded in seconds from the time of immersion. Severity of cold immersion pain was graded and indicated by the following symbols: *0* = no pain; + = mild pain; ++ = moderate pain (tolerated without difficulty); +++ = severe pain (commonly associated with grimacing, muscle tensing, occasionally with pallor and sweating).

RESULTS AND DISCUSSION

Evaluation of Spontaneous Digital Vascular Adjustments Obtained During Control Period. Average pulse volumes as low as 2.3 cu. mm. and as high as 8.4 cu. mm. were recorded in similar segments of the digits in individuals under the same ambient conditions. A high degree of consistency in a given individual observed on separate occasions was demonstrated. Average pulse volumes observed on two occasions 2 to 3 weeks apart, showed a difference of one cu. mm. or less in 10 of 14 subjects. Similarly, 10 individuals showed the same degree of spontaneous mean volume fluctuations on two occasions.

Digital Vascular Responses to Deep Respiration, Mental Arithmetic, 'Loud Noise,' and 'Pulled Hair.' The plethysmographic patterns following these stimuli were similar. Vasoconstriction developed rapidly, beginning from 3 to 5 seconds following the stimulus. Minimal pulse volumes and mean finger volumes were reached usually within 10 seconds. The vasodilatation which followed was more gradual, and varied with the degree of vasoconstriction and the nature of the stimulus. Since for a given individual the range of response to any one of these stimuli was frequently nearly as great as the range of response for the entire group, no consistent difference between individuals could be established. Hence, these responses could not be utilized in the final comparison of physiological responses with cold tolerance.

Digital Vascular Responses Associated with Cold Immersion of Feet. A number of similarities in the patterns were obtained prior to and during cold immersion of the feet (fig. 1). Immediately following the warning given 30 seconds before immersion, mean finger volume and pulse volume dropped percipitously, and then returned toward normal levels at the time of immersion. Following immersion, mean finger volume and pulse volume again dropped abruptly, reaching minimal levels usually within 15 seconds. Different subjects who showed similar degrees of vasoconstriction initially during immersion showed wide variation in the extent to which this vasoconstriction diminished during the latter part of immersion. In some individuals, almost maximal vasoconstriction was regularly maintained throughout the minute of immersion. In others values rose to control or supra-control levels during immersion. An index of the degree of return is obtained when a control pulse volume is compared with the maximal pulse volume observed in the latter part of immersion. As with the other pulse volume changes, this response has been recorded as a ratio of control level to observed change. This ratio will be referred to as the *sensitivity index* (S.I.) to cold immersion. Other ratios calculated were *a*) the control pulse volume/minimal pulse volume during the 'warning phase,' *b*) the control pulse volume/minimal pulse volume during foot immersion.

Cold immersion responses were obtained four times in each of 10 subjects and eight times in each of 14 subjects. Although there was considerable varia-

tion in response within a given subject, there were also consistent differences between individuals in all 3 of the indices: apprehension of immersion, cold immersion maximal response, and sensitivity index. (Average individual values are indicated in fig. 2.)

Blood Pressure and Pain Responses During Cold Immersion of Feet. In general, there was a rise in both diastolic and systolic values, beginning frequently during the 30-second warning phase, and proceeding to maximal val-

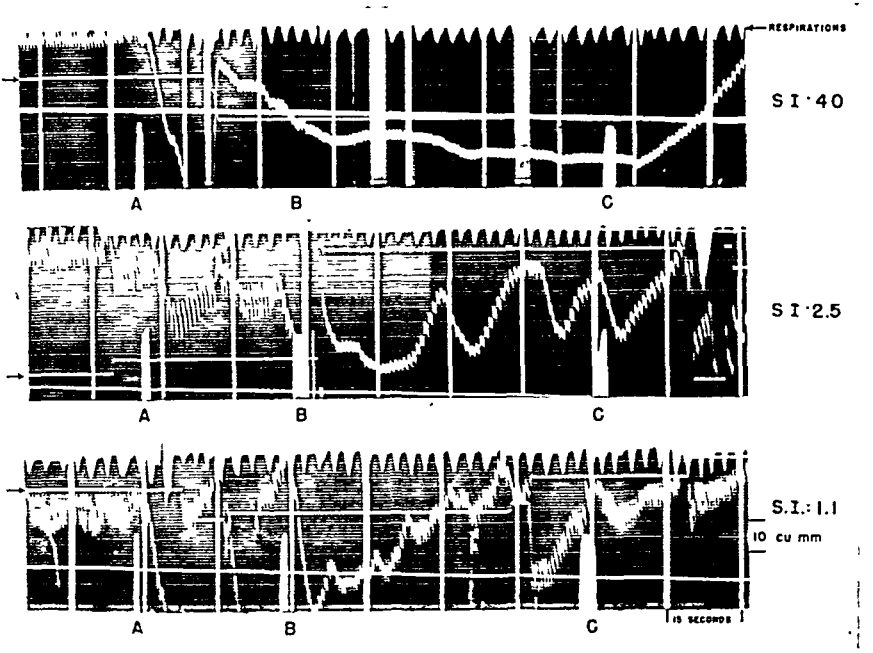

FIG. 1. DIGITAL VOLUME PLETHYSMOGRAPHIC TRACINGS obtained in 3 individuals upon immersion of both feet in ice water, illustrating range of responses observed. *A* = warning 30 seconds prior to immersion. *B* = immersion of feet in ice water. *C* = end of immersion period. Top record illustrates a sensitive individual (S.I. 4.0); bottom record illustrates an insensitive individual (S.I. 1.1). Because of the marked volume changes it was necessary to adjust base line frequently to keep the shadow of the string within margins of photo-sensitive paper. Discontinuities of base line (arrows at left of each tracing) show times at which readjustment was necessary.

ues at the end of the cold immersion period. In several instances, there were progressive drops in diastolic pressure during immersion. Although consecutive determinations on a single subject on a given day gave closely similar responses, there was considerable variation for a given subject in responses obtained after a 2-week interval. The relatively consistent finding of a decreased response of the post-bivouac group is discussed later. (Values indicated on fig. 2 are average individual values.)

Pain during cold immersion was experienced by 17 of 24 subjects. In 10,

it was severe; 2, moderate; and in 5, mild. The severity of pain was usually the same for a given individual during the 4 immersions on a single occasion.

The time of onset of pain varied considerably in an individual. The majority of subjects experiencing pain reported its onset 30 to 40 seconds after immersion. In individuals who experienced severe pain, the time of onset tended to be earlier than in the others.

Comparison of Blood Pressure Responses and Pain Experienced During Cold Immersion. Both systolic and diastolic responses to cold immersion tended to be greater in the subjects who experienced severe pain than in those experiencing mild, moderate, or no pain, e.g. all diastolic rises of greater than 20 mm. Hg and systolic rises greater than 30 were in subjects who reported severe pain. Only 3 of these had systolic rises less than 20, and only 2 had diastolic rises of less than 10. Although subjects experiencing severe pain had the greatest blood pressure rises, it may be noted that those who reported no pain, in some instances, had considerable blood pressure rises, a systolic rise of 32 mm. Hg, and a diastolic rise of 18 mm. Hg being recorded in this group.

Comparison of Blood Pressure and Digital Vascular Responses to Cold Immersion. The low degree of correlation existing between the simultaneously determined blood pressure and digital vascular responses to cold immersion suggests that the vasoconstriction occurring in the digits does not reflect the degree of vasoconstriction occurring elsewhere in the body. In the light of this finding, it is interesting to contrast the time course of the digital vascular adjustment with the time course of the blood pressure rise. Digital vasoconstriction reaches maximal levels within 10 seconds after immersion, and thereafter commonly diminishes. Blood pressure usually rises throughout immersion to maximal levels at the end of the immersion period.

Evaluation of Local and General Cold Tolerance. The evaluation of performance of the individuals could not exclude performance independent of cold stress. It was the invariable case that the 'best soldiers' performed adequately on field bivouacs under cold stress. The indices selected for separation into groups according to cold tolerance were: *a*) the difficulty experienced with frostbite, *b*) relative ability in accomplishing tasks with unprotected hands and *c*) the enthusiasm, or lack of enthusiasm of the individual for out-of-door existence in the cold, in other words, the way they 'took to' Arctic living.

Groups 1 (4 subjects) and *2* (8 subjects) comprised men who liked Arctic life and performed in superior fashion under prolonged cold stress. *Group 1* was distinguished by the fact that none of the 4 individuals included had ever experienced frostbite of any part, despite considerable exposure to extreme cold. *Group 3* (10 subjects) consisted of men who performed adequately during cold exposure. The 2 men placed in *Group 4* performed inefficiently in the cold. One was a continual source of difficulty on field bivouacs because of uncooperativeness. The other had to be brought back from a bivouac because he 'couldn't

take it.' It cannot be said that in either instance cold stress was solely responsible for poor performance. Six individuals were tested for specific manual ability in the cold.

Comparison of Results of Physiological Studies with General and Local Cold Tolerance. Consistent differences among individuals were demonstrated in 8 separate physiological indices: *1*) sensitivity index; *2*) cold immersion, maximal pulse volume reduction; *3*) apprehension of cold immersion, maximal pulse volume reduction; *4*) average pulse volume observed during control

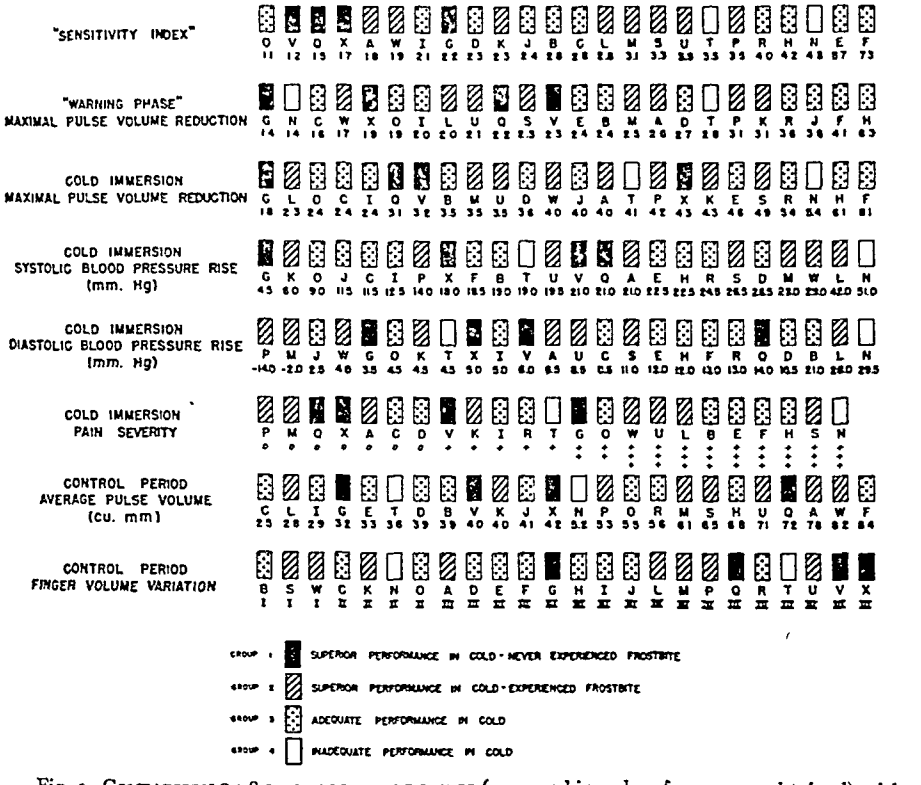

Fig. 2. COMPARISON OF 8 PHYSIOLOGICAL INDICES (arranged in order of responses obtained) with an evaluation of cold tolerance. Only average individual values of physiological indices are included.[5]

period; *5*) degree of mean finger volume variation during control period; *6*) degree of systolic blood pressure rise occurring during cold immersion; *7*) degree of diastolic blood pressure rise occurring during cold immersion; *8*) severity of pain experienced during cold immersion.

In figure 2 the indices have been separately arranged in order of the degree of the responses recorded. It should be pointed out that because of the considerable 'overlapping' of responses among individuals, the listing of the entire group in terms of degree of response does not indicate a rigid order-

[5] See footnote 2.

ing from individual to individual. The cold tolerance evaluation for each individual is indicated.

It may be seen that a single index, namely, the sensitivity index, which expresses the degree of digital vasodilatation occurring in the latter phase of cold immersion, offers a degree of correlation with the cold tolerance. If the group is divided into thirds according to S.I., the 8 least sensitive individuals include all of *Group 1* (individuals who had never experienced frostbite); 2 individuals from *Group 2* (men who had performed in superior fashion under cold stress); and 2 members of *Group 3* (men who had performed adequately

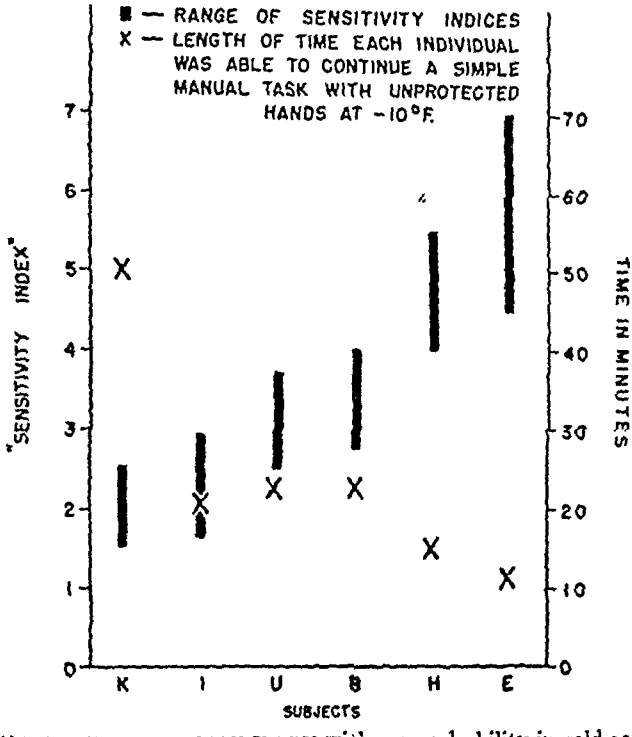

Fig. 3. COMPARISON OF SENSITIVITY INDEX with manual ability in cold as indicated by length of time an individual was able to continue a simple task with unprotected hands at −10°F. (Each value is an average of 2 separate determinations.)

under cold stress). The 2 individuals of *Group 4* are in the most sensitive third. No statistically significant difference exists between *Groups 2* and *3*.

The results of the experiment in which 6 individuals were tested for specific manual ability in the cold are compared in figure 3 with individual values for S.I. It may be seen that *K*, who had the lowest S.I. range of the 6 subjects, was able to continue a simple manual task with unprotected hands at −10°F. for 40 and 60 minutes on two occasions, while *E* who had the highest S.I. of the 6 subjects was unable to continue because of intense finger pain after 14 and 8 minutes on two occasions.

It is of interest to attempt to relate the observed digital vascular response to cold immersion of the feet to vascular responses of individuals under general cold stress, which may in turn be responsible for individual differences in

cold tolerance. In this regard individuals, who tend to vasodilate during the artificial situation of the cold immersion test, may show a similar tendency to maintain states of relative vasodilatation of the digits and other skin areas under general cold stress. The lower incidence of frostbite and superior manual ability of certain individuals in the cold might be explained, in part, by this phenomenon.

Comparison of Physiological Studies in a Group of 10 Subjects before and after a Field Bivouac. Ten men were studied before and after field bivouacs under conditions of relatively severe cold stress. A control group of 10 subjects residing in Lawrence, Massachusetts, was tested during May 1949, utilizing the same cold immersion procedure except for plethysmographic studies. Blood pressure and pain responses were noted. The tests were performed under identical constant temperature control conditions.

Of the 10 men in the bivouac group, 6 experienced pain on cold immersion before, and one after bivouac. The control group of 13 all experienced pain on both occasions. In the bivouac group, systolic rises during immersion were less after the bivouac period in 8, unchanged in one, and greater in one. Of the control group, systolic rises were less in 5, essentially the same in 4, and greater in 6. Of the bivouac group, the diastolic rise was less after bivouac in 7, the same in 2, and greater in one. In the control group, the diastolic rise was less after 2 weeks in 4 subjects, the same in 3 subjects, and greater in 4. Of the 4 subjects who experienced no pain on cold immersion either before or after bivouac, all 4 had a reduction in systolic rise after bivouac, ranging from 6 to 16 mm. Hg, and 2 out of 4 had a reduction in diastolic rise of 6 to 13 mm. Hg, respectively.

Decrease in cold immersion blood pressure rise and decrease in pain experienced during immersion has been reported by Pecora (3), in a group of 18 men studied before and after a 10-day Arctic bivouac. Our results confirm this finding. Pecora attributed the decrease in blood pressure response observed after a field bivouac to the reduction of intensity of the pain experienced. It is of interest that in the present study 4 of the subjects experienced no pain on immersion either before or after a field bivouac, but nevertheless showed significant reductions in their blood pressure responses.

None of the digital vascular indices showed any consistent change after bivouac. In the light of the definite decrease in both blood pressure response and pain intensity, this fact supports the conclusion previously expressed in this report that the digital vascular and blood pressure responses of cold immersion are for the most part independent phenomena.

SUMMARY

A variety of vascular responses, principally of the fingers, has been observed in a group of 24 men and compared with certain aspects of their indivi-

dual cold tolerance. These studies were carried out under controlled ambient conditions at Fort Churchill, Manitoba, Canada. Individuals in whom reduction of finger blood flow, during immersion of the feet in ice water, was relatively transient had, in general, a lower incidence of frostbite; they were able to work with unprotected hands in the cold for more prolonged periods than individuals in whom vasoconstriction was maintained throughout immersion of the feet in ice water. It should be stressed that, although correlation between digital vascular response and cold tolerance was demonstrated for groups of individuals, there were notable individual exceptions to the pattern. Hence, the cold immersion response of an individual cannot be regarded as a specific indication of his performance under cold stress. None of the remaining physiological indices in which consistent variation among individuals was demonstrated showed any marked relationship with cold tolerance. These included spontaneous variation in finger pulse volume and finger mean volume during a control period, finger pulse volume reduction during the warning phase prior to cold immersion of the feet, maximal finger pulse volume reduction during immersion, blood pressure rises during immersion, and severity of pain experienced during immersion. Men studied before and after a field bivouac under cold stress experienced less pain and had smaller blood pressure rises during immersion of the feet in ice water after bivouac.These changes were not observed in unexposed men.

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Occurrence in Normal Individuals of Diurnal Variations in Acuity of the Sense of Taste for Sucrose[1]

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RECENTLY EXPERIMENTS WERE REPORTED (1) demonstrating the existence in human subjects of diurnal variations in olfactory acuity. The pattern of these variations was found to be remarkably uniform and intimately connected with ingestion of food. In normal individuals, meals were found regularly to be preceded by a period of increasing and followed by one of decreasing acuity of olfaction. When a meal had been omitted a decrease in olfactory acuity could not be demonstrated. In discussing these observations the suggestion was made that the precibal increase in olfactory acuity may be related to the sensation complex of appetite and that the postcibal decrease in olfactory acuity may be related to the sensation complex of satiety. The demonstration of the existence of diurnal variations in olfactory acuity and of their dependency upon ingestion of food made it appear interesting to determine whether or not like variations exist in gustatory acuity.

A survey of literature on the subject reveals that several investigators while studying various aspects of gustation reported observations indicative of the existence of diurnal variations in acuity of the sense of taste. Reference is made to studies reported by Baryscheva (2), Salmon and Blakeslee (3) and by Floyd (4). That such variations in gustatory acuity may be attributable to certain rhythmic changes in a person's internal environment was suggested by Bellomo (5), Weiss and Pascucci (6, 7), Guidizi and Noferi (8) and by Mayer-Gross and Walker (9). The information gathered by these authors does not lend itself as evidence for the existence of such variations in acuity of the sense of taste. More recently Janowitz and Grossman (10) investigated the question at hand. In their study gustatory thresholds for salt and sugar were determined in presumably normal individuals at 10:30 A.M., shortly before and 2 hours following ingestion of freely selected noon meals. Threshold values for the taste of salt were determined in 9, and those for the taste of sugar in 10 subjects. There was but one test day for each subject. From their observations Janowitz and Grossman disclaimed the existence under normal conditions of diurnal variations in gustatory acuity, particularly in relation to sensations associated with ingestion of food. To those

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familiar with the difficulties involved in studies concerning sensory acuity the evidence presented by the authors in support of their conclusion must appear inadequate. Due to the paucity of available data the statistical analysis offered seems to be of questionable validity.

The apparent inconclusiveness of information contained in the literature regarding the existence of diurnal variations in gustatory acuity indicated the desirability of additional studies designed in order to clarify the question at hand. The present experiments were performed with this purpose in mind.

METHOD AND PROCEDURE

Gustatory thresholds for sucrose were determined by placing a measured volume (0.5 cc.) of sucrose solution on the tip of the subject's extended tongue. The solutions used had been made up with tap water and contained sucrose in concentrations ranging from 0.1 to 2.5 per cent in steps of 0.1 per cent. The lowest concentration of sucrose which just sufficed to permit instantaneous recognition of sweetness was interpreted as the measure of threshold for this gustatory quality for the subject at that time. At each determination the threshold value accepted for the subject was the lowest concentration of sucrose which produced the sensation of sweetness three times in succession. Before and between successive trials the subjects were requested to rinse their mouths with tap water. In this manner gustatory thresholds for sucrose were determined at 10:00 and 11:00 A.M. and at 1:30 and 4:30 P.M. Subjects exhibiting coating of the tongue or taking medicine for any reason were excluded temporarily from the experiment. During the tests the subjects were kept uninformed as to the concentration of the sucrose solutions used.

There were 16 individuals, 14 females and 2 males, who served as subjects. They were in apparently good health and ranged in age from 20 to 54 years. They held clerical and technical positions in this institution and worked daily from 9:00 A.M. until 5:00 P.M. As a rule they had breakfast and dinner at home at customary hours, but ate lunch in the hospital cafeteria which offered a variety of dishes so as to permit reasonably free selection of food. Lunch was served between 12 noon and 1:00 o'clock in the afternoon. On test days the subjects were requested to abstain from taking food between meals. Their statements regarding their desire for food as well as their freely selected caloric intake were recorded.

The results to be discussed are those of gustatory threshold determinations performed in all subjects on days on which the subjects observed normal food habits. Also analyzed are the results of gustatory threshold determinations made in some of the subjects on days on which the subjects omitted their noon meals.

ANALYSIS OF RESULTS AND OBSERVATIONS

Days on Which the Subjects Observed Normal Food Habits. Available for analysis are the results of tests performed in the 16 subjects on 203 test days.

The number of test days for the subjects ranged from 7 to 18, with a group average of nearly 13 days. Figure 1 shows the averages of gustatory threshold values for sucrose obtained at different hours of test days. The illustration demonstrates a decrease of the gustatory threshold values during the morning hours, an increase following ingestion of lunch and another decrease of the gustatory threshold values during the later afternoon. Variations in gustatory threshold values for sucrose of the pattern described were noted on 150 (73.9%) of the 203 days. The increase of gustatory threshold values could not be demonstrated on 10 (4.9%) of the test days. On 25 (12.3%) test days no decrease of gustatory threshold values was noted during the morning hours. On 13 (6.4%) of the test days no decrease in gustatory threshold values was demonstrable during the later afternoon. On 5 (2.5%) test days there was noted an increase of the gustatory threshold values following ingestion of lunch but a decrease of threshold values was noted neither during the morning nor during the later afternoon.

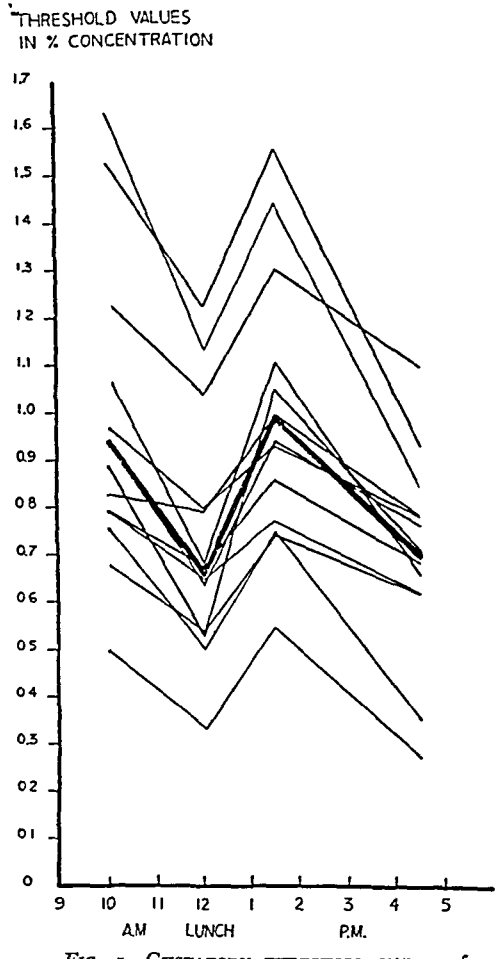

FIG. 1. GUSTATORY THRESHOLD VALUES for sucrose obtained at different hours of test days and expressed in terms of average percentage of concentration of solution. *Light lines:* for the individuals; *heavy lines:* for the group.

The nature of the study under discussion required analysis of results obtained for individual subjects. Therefore, an inquiry was made as to the significance of difference between gustatory threshold values obtained for a subject at different hours of the day. The results of these calculations are presented in table 1. The values in *Columns A*, *B* and *C* indicate the average differences expressed as percentage concentration of solution between the threshold values obtained at 10:00 and 11:30 A.M. (*A*); between the threshold values obtained at 11:30 A.M. and 1:30 P.M. (*B*) and between threshold values obtained at 1:30 and 4:30 P.M. (*C*). The values in *Column P* indicate the respective p

ability (calculated by means of Student's t value) (11) that these differences are not significantly greater than zero. Statistical convention justifies the assumption that probability values of 0.05 or less are indicative of significance. This means that differences between the averages of threshold values are significant if the probability that they are not significant is 0.05 or less.

In all subjects the gustatory threshold values in average decreased during the morning, increased following ingestion of lunch and decreased during the later afternoon. Of the 48 differences available for statistical analysis only one failed to be of significant magnitude. Reference is made to *subject 16* whose

TABLE 1. AVERAGE DIFFERENCES BETWEEN GUSTATORY THRESHOLD VALUES OBTAINED AT DIFFERENT HOURS OF TEST DAYS[1]

SUBJECT	NO. OF TEST DAYS	DIFFERENCE A (DECREASE)	P_A	DIFFERENCE B (INCREASE)	P_B	DIFFERENCE C (DECREASE)	P_C
1	18	−0.20	<0.01	+0.38	<0.01	−0.42	<0.01
2	17	−0.18	<0.01	+0.14	<0.01	−0.15	<0.01
3	16	−0.26	<0.01	+0.23	<0.01	−0.39	<0.01
4	16	−0.14	<0.01	+0.31	<0.01	−0.38	<0.01
5	16	−0.26	<0.01	+0.15	<0.01	−0.26	<0.01
6	15	−0.14	0.01	+0.21	<0.01	−0.12	0.01
7	15	−0.22	<0.01	+0.15	<0.01	−0.23	<0.01
8	14	−0.16	<0.01	+0.20	<0.01	−0.26	<0.01
9	13	−0.06	0.04	+0.15	<0.01	−0.18	<0.01
10	12	−0.15	<0.01	+0.13	<0.01	−0.13	<0.01
11	10	−0.11	<0.01	+0.13	<0.01	−0.17	0.05
12	9	−0.11	<0.01	+0.27	<0.01	−0.23	<0.01
13	9	−0.21	<0.01	+0.28	<0.01	−0.21	<0.01
14	8	−0.11	0.04	+0.11	<0.01	−0.17	<0.01
15	8	−0.40	<0.01	+0.42	<0.01	−0.46	<0.01
16	7	−0.10	0.05	+0.14	0.05	−0.05	0.45

[1] Expressed as percentage concentration of sucrose in solution.

gustatory threshold value did decrease but insignificantly during the late afternoon.

Days on Which the Subjects Omitted Their Noon Meals. In this series of experiments 5 subjects cooperated. Threshold determinations were performed in the manner described. Days on which the subjects omitted their noon meal were preceded and followed by days on which they observed normal food habits. There were 23 test days for the group on which lunch had been omitted and 67 test days on which normal food habits had been observed. For individual subjects the number of these test days ranged from 3 to 5 and from 8 to 16 respectively.

Figure 2 shows the averages of gustatory threshold values for sucrose obtained at different hours of these test days. As can be seen from the illustra-

tion there was no increase of gustatory thresold values demonstrable on the days on which lunch had been omitted. This observation held true for all 23 test days.

Again, a statistical analysis of results obtained for individual subjects appeared desirable. Therefore an inquiry was made as to whether or not the differences between averages of gustatory threshold values obtained immediately

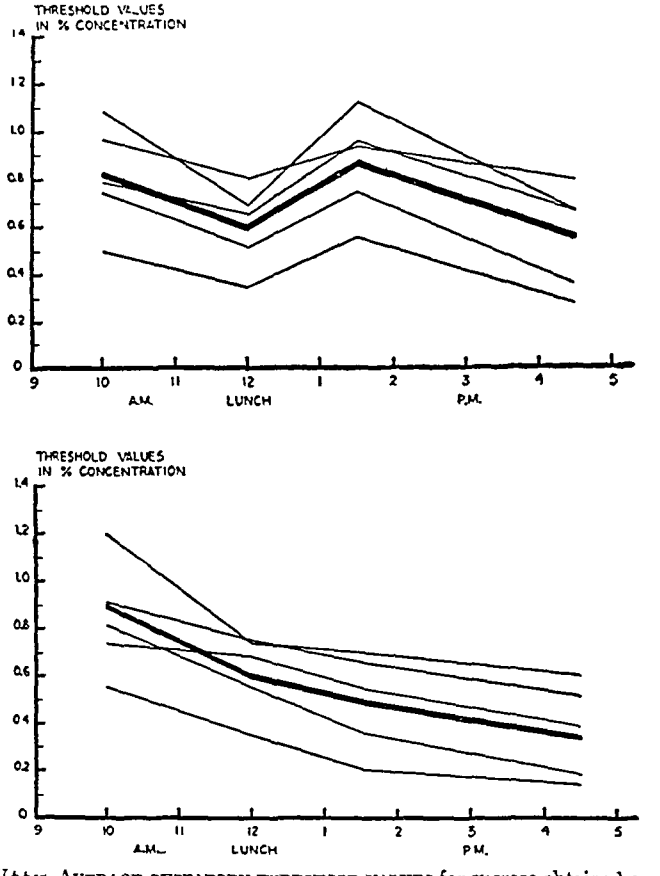

FIG. 2. *Upper.* AVERAGE GUSTATORY THRESHOLD VALUES for sucrose obtained on days on which lunch was ingested. *Lower:* Average gustatory threshold values for sucrose obtained on days on which lunch was omitted. *Light lines:* for the individuals; *heavy lines:* for the group.

before and 30 minutes after lunch time on days on which lunch had been ingested differed significantly from the differences between like averages of gustatory threshold values obtained on days on which lunch had been omitted. The results of these calculations are presented in table 2. The values in *Columns* B_1 and B_2 represent the average differences expressed as percentage concentration of solution between threshold values obtained at 11:30 A.M. and at 1:30 P.M. on days on which lunch had been ingested (B_1) and on days on which lunch

had been omitted (B_2). The values in *Column P* indicate the probability (calculated by means of Student's *t* value) that the difference between the differences referred to is not significant. As mentioned before, it is justified to assume that a difference is significant if the probability that it is not significant is 0.05 or less. From table 2 it can be seen that the difference under discussion was found to be significant for all subjects.

From the subjects' statements it was learned that noon meals were preceded regularly by a period of an increasing desire for food denoted variously by the subjects as a sensation of hunger or one of appetite. Following ingestion of the freely selected noon meals a sensation of satiety developed in all instances while the desire for food vanished.

The noon meals selected by the subjects ranged in their caloric value between 325 and 1024 calories. It should be noted that the subjects did not on all occasions choose to eat dessert at the end of their noon meals. The significance of this observation will be mentioned below.

TABLE 2. AVERAGE DIFFERENCES BETWEEN GUSTATORY THRESHOLD VALUES OBTAINED BEFORE AND AFTER LUNCH TIME[1]

SUBJECT	NO. OF TEST DAYS ON WHICH LUNCH WAS INGESTED	NO. OF TEST DAYS ON WHICH LUNCH WAS OMITTED	DIFFERENCE B_1 (INCREASE)	DIFFERENCE B_1 (DECREASE)	*P*
1	17	5	+0.14	−0.10	<0.01
2	16	5	+0.23	−0.20	<0.01
3	16	5	+0.31	−0.10	<0.01
4	14	5	+0.20	−0.14	<0.01
5	8	3	+0.42	−0.02	<0.01

[1] Expressed as percentage concentration of sucrose in solution.

DISCUSSION

Changes in threshold values for the sense of gustation indicate changes in gustatory acuity. Thus, decreasing threshold values signify an increase, increasing threshold values a decrease in acuity. Therefore, the observations described reveal that the acuity of the sense of taste for sucrose was greater before than shortly after ingestion of noon meals on 193 (95.1%) of the 203 test days. An increase in the gustatory acuity during the morning was noted on 173 (85.3%) and an increase during the later afternoon on 185 (91.2%) of the test days. The high percentages cited appear to indicate reliability of the observations. Additional confirmation of this impression can be deduced from the analysis of results obtained for individual subjects. This analysis taking into account averages of gustatory threshold values obtained for the individual subjects at different hours of test days reveals that there were demonstrable in all 16 subjects a statistically significant increase in gustatory acuity before lunch and a statistically significant decrease shortly after ingestion of the meal. The decrease

in gustatory acuity noted in all subjects during the later afternoon was found to be statistically significant in all but one of the subjects.

The evidence presented justifies the conclusion that there exist in normal individuals diurnal variations in acuity of the sense of taste for sucrose. The question whether or not like variations exist with respect to other taste qualities is being investigated in this laboratory. Preliminary observations made in studies along these lines seemingly indicate that it may be unjustified to expect uniformity in behavior of the various taste qualities.

That the decrease in acuity of the sense of taste for sucrose was dependent upon ingestion of food becomes evident from the analysis of results obtained on days on which noon meals had been omitted. This analysis shows for all subjects so tested that the changes in gustatory acuity noted after lunch time on days on which lunch had been ingested differed significantly from those noted at the same time of the day but on days on which lunch had been omitted.

Since the freely selected noon meals upon ingestion brought about a conversion of the sensation complex of appetite into one of satiety, the observations made in the present experiments may be interpreted as indicating that the precibal increase in acuity of the sense of taste for sucrose may be related to the sensation complex of appetite and that the postcibal decrease in acuity of that sense may be related to the sensation complex of satiety. This interpretation of results is supported by the fact that the decrease in acuity of the sense of taste for sucrose failed to occur when the conversion of the sensation complex of appetite into one of satiety had been prevented by omission of noon meals.

The mechanisms by means of which food produces a decrease in acuity of the sense of taste for sucrose are being subjected to further investigation. Phenomena of adaptation and fatigue cannot explain this effect of food because the decrease in sensory acuity described occurred regardless of whether or not the meal had sweets in its composition.

SUMMARY AND CONCLUSIONS

Experiments are described which demonstrate the existence in normal individuals of diurnal variations in acuity of the sense of taste for sucrose. Freely selected meals were found to be preceded by a period of increasing and followed by one of decreasing acuity of that sense. When meals had been omitted the decrease in acuity failed to occur. It was suggested that the increase in acuity of the sense of taste for sucrose may be related to the sensation complex of appetite and that the decrease in acuity of this sense may be related to the sensation complex of satiety.

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Phreno-Vagal Anastomosis in the Dog[1]

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FORMATION, RECURRENCE AND AGGRAVATION of peptic ulcer have been connected with emotional effects conveyed to the stomach and duodenum by the vagus nerves. It has not been possible so far, to produce ulcer by emotional factors in the experimental animal. We felt that we would come nearer to an approach to this problem, if we could send impulses to the stomach through the vagi at short intervals, day and night, by anastomosing the left central phrenic nerve to the distal end of the left vagus trunk. If a functioning anastomosis developed, the impulses from the respiratory center would produce vagal hyperactivity by bombarding the end-fibers of the vagus nerve more continuously. Cannon *et al.* (1) have used similar reasoning when they anastomosed one phrenic nerve to the sympathetic trunk.

The first dog, operated in 1934, was observed 10 months after the proximal left phrenic nerve had been anastomosed to the distal left vagus nerve. While standing quietly, suddenly the abdomen distended enormously, and the dog died within a few minutes. No swallowing movements were seen during this period. Immediate autopsy revealed a tremendous dilatation of the stomach, which filled practically the entire abdomen and which had pushed the diaphragm high into the chest. The stomach was filled with air. The mucosa just below the cardia showed 10 small, punched out ulcers, arranged in a circular fashion.

Normal mongrel dogs were anesthetized with i.v. pentobarbital sodium. In an aseptic operation the left phrenic was sectioned just above the diaphragm, and the left vagus trunk just below the hilus of the left lung. Then the proximal stump of the phrenic and the distal stump of the vagus nerve were approximated carefully to produce end to end contact, and they were sewn together with their sheaths and surrounding tissues. In a number of animals, both nerves were sectioned, and the phrenico-vagal anastomosis was performed one to 2 months later at a second operation.

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Observations were carried on from one to 20 months after the anastomotic operation, to observe diaphragmatic activity and gastric motility and emptying times (2). During the first 12 to 14 weeks post-operatively, fluoroscopic observations were made weekly, then at monthly intervals. Acute experiments were done on 4 of the dogs, 14, 18, 20 and 20 months, post-operatively. The animals were anesthetized with sodium pentobarbital, artificial respiration was instituted, and the left chest and abdomen were opened. Gastric motility was recorded with the balloon method. The left phrenic and vagus nerves were stimulated above and below the anastomosis respectively, using various strengths of current of the secondary coil of a Gorell inductorium. At the termination of all experiments, complete autopsies were performed, and specimens for microscopic study were taken from the left phrenic nerve, the anastomosis, the vagus nerve below the anastomosis, and from identical sites of both diaphragms.

RESULTS

One dog with a one-stage phrenico-vagal anastomosis died of pneumonia one week after operation. One dog died one month after operation with extensive gastro-malacia; this animal had been subjected to bilateral complete vagotomy at the hilum of the lungs and a left side phrenico-vagal anastomosis. One dog died during a third-stage operation, 7 months after section of the left vagus and 5 months after phrenico-vagal anastomosis. One dog died 15 months after a one-stage phrenico-vagal anastomosis; this animal had lost much weight due to anorexia, and autopsy did not reveal a cause of death except wasting. In all dogs with phrenicotomy, gastric emptying times were shortened considerably, but returned to normal within 4 and 12 weeks. No left diaphragm was seen to re-activate up to 20 months after phrenico-vagal anastomosis. Except the dog with ulcers in the cardia and the one with gastromalacia, in no animal were abnormal changes found in the esophagus, stomach or duodenum.

Four acute experiments were performed 14, 18, 20 and 20 months after the operation for nerve anastomosis. The left diaphragm was thin and atrophied and showed no motility, confirming previous observations (3). The stomachs showed no motility synchronous with the respiratory motion of the right diaphragm. When the left phrenic nerve was stimulated above the anastomosis, an increase in respiration and elevation in blood pressure occurred. When the nerve was cut proximal to the electrode, this reflex was abolished. In 2 dogs, 14 and 20 months after the phrenico-vagal anastomosis, stimulation of the phrenic nerve above the anastomosis did not produce gastric or diaphragmatic motility. However, when the vagus nerve below the anastomosis was stimulated, gastric motility was increased (fig. 1). Sections showed neuromas at the site of the anastomosis, and no phrenic fibers crossing into the vagus trunk. Below the anastomosis normal fibers were seen in the vagus trunk.

In 2 dogs, 18 and 20 months after operation, a functioning anastomosis had established itself, as evidenced by contractions of the stomach when the phrenic nerve was stimulated above the anastomosis. This was still observed after the phrenic nerve was cut proximal to the electrodes (fig. 2). In these 2 dogs, serial sections of the phrenic nerve above the anastomosis, of the anastomosis itself, of the vagus nerve below the anastomosis and of the left diaphragm, revealed degenerating and regenerating nerve fibers, as well as an atrophied left diaphragm, replaced by fibrous tissue and fat.[2]

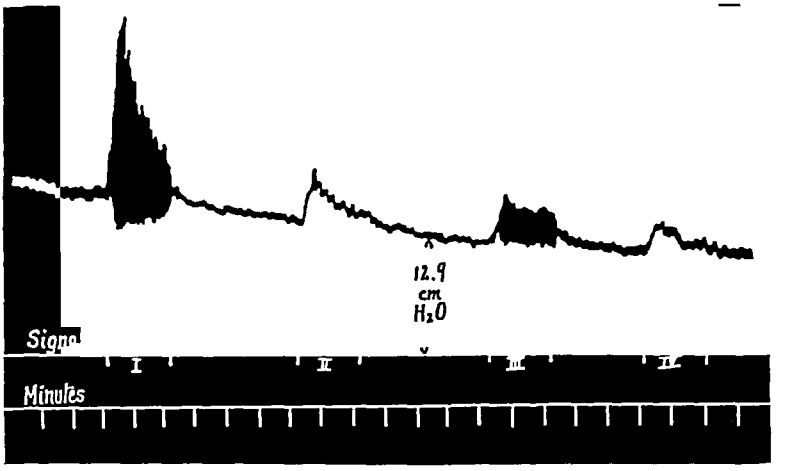

FIG. 1. BALLOON RECORD OF GASTRIC MOTILITY of *dog 6*, taken 20 months after phrenicovagal anastomosis. I: Left phrenic nerve stimulated high above anastomosis (hilum), 2-volt primary. Increased rate and depth of respiratory movements; no stomach motility. II: Left vagus trunk stimulated below anastomosis, 10-volt primary; gastric motility. III: As in no. I; no stomach motility. IV: As in no. II; gastric motility.

DISCUSSION

We have not been able to reproduce the acute dilatation and ulcers of the stomach following phrenico-vagal anastomosis observed in our first experiment. Section of the left vagus trunk and severance of all connections between the left and the right vagus trunks did not appear to produce gross alterations in gastric motor function. Section of the left phrenic nerve leads to a disturbance of the function of the stomach which we have described previously, and which disappears within 4 to 12 weeks (4). If the left phrenic nerve had been sectioned completely, the left diaphragm degenerated, and it never recovered its respiratory function (3). The paralyzed left diaphragm seems to predispose to increased aspiration of air into the stomach which process, however, readjusts itself within no more than 11 months (3). High section of the left vagus trunk, in addition to section of the left phrenic nerve, may occasionally lead to dis-

[2] We acknowledge the help of Dr. O. Saphir, Pathologist, of Michael Reese Hospital.

turbances of the lower esophagus, the diaphragmatic pinchcock, the cardia, and the stomach, and such masses of air may be aspirated into the stomach, that acute dilatation of that organ may occur with a fatal outcome. This is the only explanation we can offer for the observation on one dog mentioned above. Unfortunately, we do not have data on nervous conduction across the phrenico-vagal anastomosis in that animal.

The experimental results on the conducting phrenico-vagal anastomoses indicate only that a relatively weak induced current was able to set up an impulse in the phrenic nerve which, traveling across the anastomotic junction and through the vagus to the stomach, produced gastric motility. Conduction across

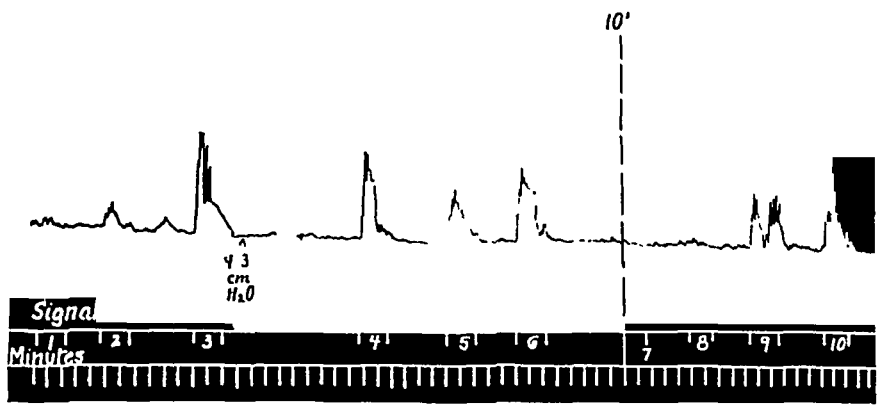

FIG. 2. BALLOON RECORD OF GASTRIC MOTILITY OF *dog 5*, taken 20 months after phrenicovagal anastomosis. 1: Left phrenic nerve stimulated high above anastomosis (hilum), 2-volt primary; no stomach motility. 2: Same as no. 1, 10-volt primary. 3: Left phrenic nerve stimulated 2 cm. above anastomosis, 2-volt primary; distinct gastric contraction. 4: Same as no. 3, 10-volt primary. 5: Left vagus trunk stimulated 2 cm. below anastomosis, 2-volt primary; distinct gastric contraction. 6: Same as no. 5, 10-volt primary; distinct gastric contraction. 7: Left phrenic nerve cut 5 cm. above anastomosis. 8: And stimulated above the section described in no. 7, no stomach response; 10-volt primary. 9: Left phrenic nerve stimulated above anastomosis, but below section described in no. 7; distinct stomach motility; 10-volt primary. 10: Left vagus trunk stimulated below anastomosis, 10-volt primary; distinct stomach motility.

the anastomosis is indicated also by the histologic picture of normal nerve fibrils running from the phrenic nerve into the vagus nerve. There was no indication of physiological activity. Following the establishment of a functioning anastomosis between the central left phrenic nerve and the peripheral left vagus trunk, the rhythmic discharges of the respiratory center should be deviated into the left vagus nerve, and hence to the stomach. It is possible, that the respiratory center stopped sending impulses during the long interval between end organ-muscle cell (diaphragm) inactivity and formation of the phrenico-vagal anastomosis. Perhaps the respiratory impulses were insufficient in strength and individual duration to have an effect on the smooth muscle of the stomach.

The correlation between the finding of neurofibrils crossing the anasto-

mosis from the phrenic nerve to the vagus trunk, and gastric contraction following electric stimulation of the proximal phrenic nerve, and the absence of gastric contractions when neuromas had formed and no neurofibrils crossed the anastomosis, is striking. One wonders, whether certain effects of the functional anastomoses may have been missed, because they were not distinct, or because they were slow in forming.

The literature on nerve anastomosis indicates that regenerating fibers of one nerve will grow into the sheath of the lower segment of another nerve, though less readily than into its own sheath, and even the fibrils of a sensory nerve will grow into the distal segment of a motor nerve, and vice versa. The proximal end of the hypoglossal or spinal accessory nerves have been anastomosed to the distal end of a paralyzed facial nerve, with functional result (5). Cannon, Binger and Fitz (1) united the phrenic nerve of cats to the cervical sympathetic trunk low in the neck and later observed a rise in metabolism, nervous excitability, and increased heart action. These effects were attributed to stimulation of the thyroid by impulses discharged from the respiratory center. This experiment was repeated by Horrax (6) and by Friedgood and Cannon (7) with essentially the same result. Ballance and Duel (8) anastomosed the central end of the hypoglossal nerve of cats to the peripheral cut end of the cervical sympathetic, and reported that normal pupillary reactions were restored. Restoration of function does not follow the union of a motor with a sensory nerve, nor of a cholinergic with an adrenergic nerve (5). It has been shown by Tello (9) in animals and by Duel (10) in man that, after a nerve has been severed, a better functional result is obtained, if from 2 to 3 weeks are allowed to elapse before the divided nerve is sutured. We have used this technique of delayed anastomosis between the phrenic and vagus nerves, but it apparently offers no advantage over immediate performance of the anastomosis.

We have described above that, 20 months after section of the vagus, stimulation of the left vagus trunk below a non-functioning phrenico-vagal anastomosis was followed by gastric motility. This effect persisted after complete section of the right vagus trunk. We assume, that functioning fibers in the left vagus trunk were derived from connections with the right vagus nerve.

SUMMARY

In normal dogs, the central end of the cut left phrenic nerve was anastomosed with the peripheral stump of the cut left vagus trunk, and the animals were observed for 14 to 20 months. Phrenicotomy alone produced faster emptying of the stomach and a large air bubble in the relatively dilated stomach. This disappeared within a few months. The left diaphragm remained inactive and degenerated in every animal.

Acute experiments were performed 14, 18, 20, and 20 months after the

operation for phrenico-vagal anastomosis. Stomach motility was observed and recorded, and the proximal end of the phrenic nerve was stimulated with induced current. In 2 animals, this stimulation was followed by the appearance of gastric motility. Sections of the region of the phrenico-vagal anastomosis of these animals showed that neuro-fibrils had grown from the phrenic nerve into the vagus nerve. No activity of the stomach was detected which would indicate that respiratory impulses from the phrenic nerve affected the stomach. In 2 other dogs, stimulation of the proximal left phrenic nerve did not elicit gastric motility. Histologic study revealed only degenerated nerve fibers at the phrenico-vagal anastomosis, and no neurofibrils could be seen connecting the proximal phrenic to the distal vagus stump.

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In Vivo Measurement of Body Fat and Body Water in a Group of Normal Men[1,2]

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IN RECENT YEARS it has become increasingly apparent that no part of the human body may be considered truly inert. However, if attention be limited to specific physiological processes, it appears that many of these processes occur predominantly in the water phase of the body while the oil or fat phase shows no evident participation. Consequently, there is a widespread need in both the research laboratory and the clinic for a practical method of estimating the relative proportions of water and free fat in the human body *in vivo*. Such a method would also provide a useful system for classifying individuals. Welham and Behnke (1) have clearly demonstrated the inadequacies of height-weight tables for such classification and selection.

Studies of total body specific gravity led Behnke to the conclusion that the body can be divided into a fat-free portion ('lean body mass') of constant gross composition, and a variable quantity of fat (2). Data obtained by direct measurement on diverse small mammals supported this concept (3). It followed that fat, with its low specific gravity (approx. 0.92), is the primary variable which determines individual body density. Thus, total body fat may be accurately estimated from body specific gravity, a procedure which has been validated on guinea-pigs (4) and white rats (5). Its application to man is based upon these (4–6) experimental studies. Since the lean body mass may be considered to be relatively constant with respect to per cent body water (3), once knowing

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[1] The opinions or assertions contained herein are the private ones of the writers and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

[2] Most of the material in this paper was presented in exhibit form at the Annual Meeting of the Federation of American Societies for Experimental Biology, Atlantic City, N. J., April 17–21, 1950.

the actual value of this constant, it becomes possible to estimate total body water from the fat content (4) and conversely, total body fat from the water content.

Evidence has been presented that antipyrine is distributed uniformly throughout the body water (7) and that accurate and practical methods are available for measuring its dilution after injection into the body (8). Messinger and Steele (9) have compared the specific gravity and antipyrine methods for the estimation of body composition on 9 subjects. The specific gravity range covered by these subjects is from 1.021 to 1.064 whereas values as high as 1.097 have been obtained in the normal male population (10). The present report is an extension of the work of these authors to a more adequate series of men.

METHODS

Eighty-one men ranging in age from 18 to 46 years were used as subjects. They are not to be considered a random sample of the male population, for about half of the group were highly selected naval divers. Special effort was also made to obtain extremes of body habitus and these, therefore, are probably better represented in the present sample than in the naval service at large. Whenever possible each subject's specific gravity and body water were both determined on the same day.

Specific Gravity. Body specific gravity was determined by the method of underwater weighing. The difference between body weight in air and body weight in water at maximal expiration, when corrected for the residual lung volume, was used to calculate gross body volume and body specific gravity. Details of the application of this method to man have been adequately described by Behnke, Feen and Welham (10). The residual air volume was determined in all subjects by either the method of nitrogen (11) or helium (12) dilution. In 38 subjects both methods were used. The per cent body fat was calculated from the specific gravity by the equation of Rathbun and Pace (4):

$$\% \text{ Body fat} = 100\left(\frac{5.548}{\text{sp.gr.}} - 5.044\right) \qquad (1)$$

Body Water. Body water was determined by the antipyrine technique of Soberman *et al.* (7). The individual antipyrine doses varied from 848 to 1250 mg., administered intravenously in 50 ml. of sterile water. Although one-quarter of the number of subjects were in the fasting state, and the remainder were allowed their usual food and fluid intake, there was no apparent significant difference between the results of the 2 groups. No attempt was made to restrict the activity of the subjects during the test period.

Blood samples were obtained at 2, 3 and 5 hours in some subjects and at 3, 4 and 5 hours in others. The latter procedure was more satisfactory in that a rare subject will show inadequate distribution of antipyrine at 2 hours.

The plasma concentrations of antipyrine were determined according to the precipitation procedure of Brodie *et al.* (8), and the optical densities of the solutions were read in a Beckman ultraviolet spectrophotometer at 350 mμ. The data were plotted on semi-logarithmic paper, and the plasma concentration at zero time was obtained by extrapolation. This value was then corrected for 8 per cent plasma solids to obtain the plasma water level.

RESULTS

The entire body of collected data is too large to be presented here. Therefore, the results with 10 subjects are shown in table 1, and table 2 summarizes all of the data in the form of means and extremes. Figure 1 shows the relation-

TABLE 1. SPECIFIC GRAVITY AND ANTIPYRINE RESULTS ON 10 SUBJECTS, INCLUDING THE EXTREMES OF SPECIFIC GRAVITY AND PER CENT WATER IN THE LEAN BODY MASS

SUBJECT	BODY WT.	SPECIFIC GRAVITY	% FAT		% WATER		PER CENT WATER IN LEAN BODY MASS
			From[1] sp.gr.	From[2] antipyrine	From[3] sp.gr.	From antipyrine	
1	60.6	1.100	0	0.3	72.0	71.6	71.6
11	76.8	1.087	6.0	11.6	58.3	63.5	67.8
23	79.1	1.080	9.3	7.0	67.6	66.8	73.8
29	75.9	1.078	10.3	1.4	64.9	70.8	79.0
48	70.9	1.063	17.5	17.5	59.2	59.2	71.7
49	91.3	1.063	17.5	23.8	59.2	54.7	66.3
68	71.4	1.054	22.0	17.3	56.1	59.4	76.1
78	98.6	1.040	29.1	29.4	51.0	50.7	71.5
80	98.1	1.034	32.1	34.1	48.8	47.3	69.5
81	97.7	1.022	38.4	40.1	44.4	43.0	69.9

[1] Calculated from the equation of Rathbun and Pace (4).
[2] Using the mean value of 71.8% water in the lean body mass, obtained in this series of 81 subjects.
[3] Using the modified equation of Pace and Rathbun; see *equation 3*.

ship of specific gravity to per cent body water by the antipyrine method in all subjects.

The subjects in table 1 are arranged in the order of decreasing specific gravity. *Subjects 1* and *81* represent the extremes of specific gravity, and *subjects 29* and *49* embrace the limits of variation with respect to the per cent water in the lean body mass. On each subject calculations of the per cent body fat from the specific gravity (*equation 1*) and per cent body water from the antipyrine results (7) were carried out. From these two values the per cent water in the lean body mass *of each subject* was calculated. The individual values for the per cent water in the lean body mass are shown in the last column of table 1. Table 2 shows that the mean per cent water in the lean body mass is 71.8 ±0.33 (S.E.).

Using this mean value of 71.8 per cent, the body fat was calculated from antipyrine results (*equation 2*) and the body water from specific gravity (*equation 3*).

$$\% \text{ Body fat} = \frac{100\left(\text{body wt.} - \frac{\text{wt. body water}}{0.718}\right)}{\text{body weight}} \qquad (2)$$

$$= \frac{100\,(71.8 - \% \text{ body water})}{71.8}$$

$$\% \text{ Body water} = 100\left(4.340 - \frac{3.983}{\text{sp. gr.}}\right) \qquad (3)$$

Equation 3 is a modification of the equation of Pace and Rathbun (3), obtained by replacing 73.2 with 71.8 as the per cent water in the lean body mass.

The calculated values for body fat and body water in columns 4, 5, 6 and 7 of table 1, indicate close agreement between the results of the 2 methods. (Spearman's rank-order correlation = 0.900.)

In figure 1, per cent body water by antipyrine is plotted against body specific gravity for all subjects. For theoretical reasons (6) the equation describing the relationship between body water and specific gravity is hyperbolic (*equation 3*). The line through the points represents the least-squares hyperbola. The equation for this line is:

$$\% \text{ Body water} = 100\left(4.317 - \frac{3.960}{\text{sp. gr.}}\right)$$

The curve for the modified equation of Pace and Rathbun (*equation 3*) is identical, within experimental error, with this hyperbola.

DISCUSSION

The experimental data presented above validate the antipyrine method as a procedure for the indirect estimation of the fat content of the body. Total body fat and total body water were calculated for all subjects on the basis of the antipyrine and the specific gravity methods. The close agreement between the 2 methods is evident in tables 1 and 2. (Spearman's coefficient for the rank-order correlation = 0.900.) Finally, the standard error of estimate for calculating body specific gravity from antipyrine data was found to be ±0.007 specific gravity units. Thus, in calculating per cent body fat from the percentage of body water (antipyrine), the error will exceed ±3.8 per cent fat in only one-third of the cases. This extends the field of application to include old and debilitated subjects, children, clinical patients who are, for the most part,

incapable of the exertion and cooperation required for the determination of body volume by displacement of water.

In table 2, the mean per cent water in the lean body mass of normal men is given as 71.8. The variation between individuals is relatively small, with a standard deviation of 2.9 per cent. Consequently, it is probably justifiable to regard 71.8 as a physiological constant for normal men in the age groups studied. The data on small mammals of several species summarized by Pace and Rathbun (3) give a mean value for water in the lean body mass of 73.2 per cent. Although per cent water in the lean body mass may be constant for individuals of the same species, age and sex, it may vary among species, possibly because of differences in the percentage of solid constituents, primarily the skeletal mass.

TABLE 2. SUMMARY OF SPECIFIC GRAVITY AND ANTIPYRINE DATA OBTAINED ON 81 SUBJECTS

MEASUREMENT	MEAN	RANGE
1) Age	26.6	18–46
2) Body weight (kg.)	75.3	53.6–102.7
3) Specific gravity	1.068	1.022–1.100
4) Body fat from specific gravity (%)	15.0	0–38.4
5) Body fat from antipyrine (%)[1]	15.0	0–40.1
6) Body water from specific gravity (%)[1]	61.0	44–72.0
7) Body water from antipyrine (%)	61.1	43–72.9
8) Water in lean body mass (%)	71.8	66.3–79.0
Standard error (%) of no. 8	±0.33 Standard dev. ±2.99	

[1] These calculations are based on the mean of 71.8% water in the lean body mass.

SUMMARY

Determinations of body specific gravity by underwater weighing and of body water content by the antipyrine method were carried out on a group of 81 normal male subjects selected to include representatives of the extremes of body habitus. The following pertinent data were obtained:

Specific gravity.....Mean 1.068, range 1.022 to 1.100
Per cent body fat (from specific gravity).....Mean 15.0%, range 0 to 38.4%
Per cent body water (from antipyrine).....Mean 61.1%, range 43 to 72.9%
Per cent water of the lean body mass.....Mean 71.8%, range 66.3 to 79.0%

The per cent water in the lean body mass (71.8%) may be considered a physiological constant for normal men. Its standard error is ±0.33 per cent and the standard deviation among individuals is ±2.9 per cent. Since the lean body mass may be considered to be of relatively constant composition with respect to nitrogen and water (3), it becomes possible to determine total body

water from the fat content (4) and conversely, total body fat from the water content.

Substitution of the antipyrine method for the specific gravity measurement is considered a valid means of eliminating the subject cooperation required by the latter procedure. The standard error of estimate for calculating body fat from antipyrine data is ±3.8 per cent fat.

The authors acknowledge the cooperation of the 81 subjects used in this work, and the kindness of Cdr. G. G. Malumphy of the Naval Experimental Diving Unit for placing

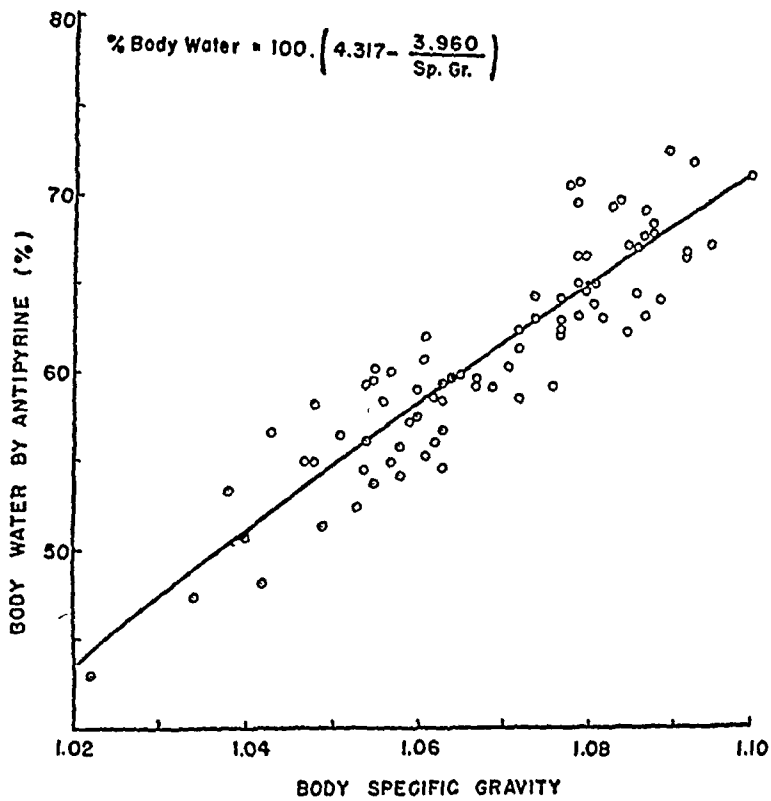

Fig. 1. THE PERCENTAGE OF BODY WATER as determined by antipyrine is plotted against body specific gravity for each of the 81 subjects. The equation for the line was obtained as explained in the text.

his personnel and facilities at our disposal. We also wish to recognize the assistance of Drs. John Flynn and M. F. Morales and the technical aid of J. J. MacArthur, HMl, D. L. Carr, HMl and M. P. Parola, HMl.

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Heat Production and Energy Requirements of Tropical People

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GALVÃO (1, 2) HAS RECENTLY INVESTIGATED the heat production of lean and well proportioned Brazilian men and has deduced that the total calories produced per hour under basal conditions are not porportional to the body surface area, but that they depend upon the 'metabolically active weight,' which can be expressed as $W^{0.83}$ for lean men and $W^{0.78}$ for well proportioned men. In this paper are presented results which strongly support Galvão's findings. These results have been collected over the past two years from observations on Ceylonese males and females of various ages, living in Colombo. In addition to these estimations of the basal metabolism of Ceylonese adults and children, the energy production by male children during play periods has also been determined. From these data, we have tentatively calculated the calorie requirements for Ceylonese and have compared them with the estimated calorie values of the foodstuffs consumed by groups of Ceylonese subjects.

METHODS

All the subjects were Ceylonese and the groups studied were 50 male adults (medical students aged 21 to 26 years), 25 female adults (medical students aged 20 to 26 years), 25 schoolboys aged 18 years, 25 schoolgirls aged 18 years, 25 schoolboys aged 14 years, 25 schoolgirls aged 14 years, 25 schoolboys aged 10 years and 25 schoolgirls aged 10 years. They had all been previously medically examined and passed as healthy.

The basal metabolism was determined by the Douglas-bag technique using a mouthpiece and nose-clip for the adult medical students and a half mask, with inflated rubber edges, for the younger subjects. Determinations were made between 7:30 and 9:30 A.M. with the subjects fasting, 13 to 15 hours after the previous meal. The subjects lay on a bed for 30 minutes, then the mouthpiece with nose-clip or the mask was fitted and 30 minutes later the expired air was collected for 10 minutes. The inspired air was outdoor air and the temperature of the room varied between 26.5° C. and 27.8° C., with a mean temperature of 27.3° C., throughout the experiments. The volume of the expired air was measured in a compensated and controlled spirometer and dupli-

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cate samples of the expired air were analyzed with a Haldane apparatus. Repeated estimations, at intervals of 3 or 4 days, were made on each subject until consistent values were obtained. In a few cases this required as many as 5 estimations.

The accuracy of the gas analyses was controlled by analyses of outdoor air at frequent intervals; the maximum difference between the combined $CO_2 + O_2$ percentage estimations and the theoretical values did not exceed 0.03 per cent.

The rate of metabolism in calories was calculated from the estimated R.Q. using the tables of Zuntz and Schumberg (3) and the surface area of each subject was determined by the du Bois' chart.

An estimation of the metabolism of schoolboys (aged 10 years and 14 years) while playing in their school compound was also made. This compound is overlooked by the author's laboratory and repeated, if casual, observations suggested that the character of the play activity was repetitive both from day to day and during the play period of any one day. Therefore, a measurement of the rate of metabolism during a short period (20 minutes) of activity will give a rough estimate of the metabolic rate during any play period. The estimations were made by collecting the expired air with a Douglas bag and a half-face mask, every effort being made to prevent air leakage. The estimations were made between 2 and 4 P.M. each day. The routine followed was to allow four boys to wear the mask and bag for one hour (10 minutes' rest, 20 minutes' play, 30 minutes' rest) each day for 5 consecutive days, and to sample and measure the expired air on the 4th and 5th day. The collection of expired air was made during the 20 minutes of play and for 30 minutes while resting immediately after the play. The analyses were made in exactly the same manner as described for the basal experiments. In all, 25 boys aged 10 years and 25 boys aged 14 years submitted to this procedure. They had all previously had their basal metabolic rates measured so that this experience plus the 3 days of wearing the apparatus without sampling had accustomed them to the mask before the actual measurements were made on the 4th and 5th days.

From the total respiratory exchange during the play and the recovery from play, the calorie output per hour by each boy has been calculated. By subtracting from this figure the corresponding estimated basal heat production, the energy production in excess of the basal rate during play has been derived.

The mean annual temperature in Colombo is 80.5° F., with a normal variation from the lowest monthly minimum, 71.8° F. in January, to 88° F. in March as the highest monthly maximum temperature. These are the mean temperature figures for the past 21 years. The mean annual humidities are 74 per cent in the day and 90 per cent at night. The monthly variations in day humidity are from a minimum of 65 per cent in February and March to a maximum of 79 per cent in June. The night humidities vary from 87 per cent

in June, July and August to 93 per cent in April and November. These are the mean figures for the past 30 years.

RESULTS

The detailed figures for each subject are presented in tables 6 to 13.[1] These data have been analyzed statistically and the relationship between heat production per hour (c) and body weight (W) and between heat production (C) and body surface area (S) (du Bois) have been calculated for each age group and each sex. Regression lines have been adjusted to the actual data and also to the logarithms of the data and, by analyses of the variances of these lines, the most satisfactory are found to be those represented by the general equations, $C = a_1 W^{b_1}$ and $C = a_2 S^{b_2}$. The particular values for each age and sex have been calculated by the method of least squares and are shown in table 1.

For the relationship between total calories and body weight, the exponent b_1 (which is the regression coefficient of the equation $\log C = \log a_1 + b_1 \log W$) is remarkedly constant from age to age and from sex to sex. Statistically, there is no significant difference between these various regression coefficients and it would seem that, for both sexes and at various ages, the rate of energy production of Ceylonese while resting and fasting can be represented by the general equation, $C = a_1 W^{0.79}$. If we assume that $W^{0.79}$ represents the metabolically active weight of the individual, then a_1 will be the heat production per unit of metabolically active weight. For both sexes, this factor a_1 has a greater value in the younger age groups, i.e. during growth. Ceylonese girls reach maturity and cease to grow earlier than the boys and, in conformity with this, the factor a_1 in the female groups reaches adult values at an earlier age too.

It is further evident, from table 1, that the relationship between heat production and weight is much closer for every group than that between heat production and surface area. If the heat production were strictly proportional to the surface area then we should expect the exponent b_2 in the equation $C = a_2 S^{b_2}$ to have a value of 1.00. The observed values for b_2 are statistically different from 1.00 in the following groups: male 10 years ($P = 0.02$), female 18 years ($P = 0.02$) and female 21 to 25 years ($P = 0.001$). Probably because of the relatively large variance of b_2, however, the values for the other groups are not significantly different from 1.00. Therefore, our results do not permit us to state that the basal heat production is not related to surface area at all ages, although it would seem that this heat production is more closely correlated with a factor of the body weight which can be expressed in general, by $W^{0.79}$.

[1] For tables 6 to 13 order Document 2852 from American Documentation Institute, 1719 N Street N.W., Washington 6, D. C., remitting $0.50 for microfilm (images 1 inch high on standard 35 mm. motion picture film) or $0.50 for photocopies (6 x 8 inches) readable without optical aid.

Another method of considering the problem is, as Galvão (1) has done, to express the surface area as a function of the body weight, $S = W^{b_3}$. On this basis, the exponent b_3 has the following mean values for our groups of subjects:

AGE IN YEARS	VALUE OF EXPONENT b_3	
	MALE	FEMALE
10	0.70	0.70
14	0.70	0.64
18	0.94	0.79
21–25	1.03	0.70

Only in the case of one group, females aged 18 years, does the value of b_3 approach the observed values of b_1 (table 1). This is further suggestive evidence that the factor, W^b, from the equation $C = a_1 W^b$, is not an expression of the surface area of the body.

So far these results are very similar to those reported by Galvão (1, 2) for Brazilian men, whose heat production was found to be proportional to $W^{0.83}$ in the case of lean men and to $W^{0.78}$ for well proportioned men. No distinction between lean and well proportioned subjects has been made in the above analysis of the data from our groups of subjects. The number of well proportioned subjects by Galvão's method of differentiation, was relatively small in most of the groups:

AGE IN YEARS	MALES	FEMALES
21	16/50	4/25
18	5/25	17/25
14	7/25	5/25
10	15/25	13/25

In those groups (males 21–25 years, females 18 years, males 10 years, females 10 years) where the distribution was such as to warrant further analysis, the relationship between weight and heat production for the two physique types has been calculated (table 2).

In all groups the exponent b is greater for lean subjects than for the well proportioned, although only in the group of females aged 10 years is this difference statistically significant. This agrees with the figures given by Galvão (*loc. cit.*) and can be interpreted to mean that well proportioned subjects have a lower metabolically active weight than have lean men. Further, for all groups, the factor a_1 is greater in the well proportioned subjects; that is, the heat production per unit of metabolically active weight is greater for well porportioned people than for lean people.

ENERGY PRODUCTION DURING PLAY

The excess energy production due to play activity by the schoolboys aged 10 to 14 years is given individually in tables 10 and 12. The relationships be-

tween this energy production and body weight or body surface area have been calculated and can be represented by the following equations.

Boys aged 14 years

Play calories $= 2.155\ W^{0.969}$ ($\sigma b_1 = 0.0064$)
Play calories $= 52.97\ S^{1.116}$ ($\sigma b_2 = 1.532$)

Boys aged 10 years

Play calories $= 2.127\ W^{0.992}$ ($\sigma b_1 = 0.0131$)
Play calories $= 45.43\ S^{1.663}$ ($\sigma b_2 = 1.176$)

(σb_1 = standard deviation of exponent of W; σb_2 = standard deviation of exponent of S)

It is evident, from these equations, that the energy, surplus to basal, produced during play is, within the limits of experimental error, directly proportional to the body weight. This is to be expected because in this instance the play consisted of running and walking, i.e. solely in the movement of the body weight.

DISCUSSION

The results presented for the basal heat productions of Ceylonese male and female subjects of various ages agree closely with those of Galvão (1, 2) in that he also found that Brazilians living in the Tropics had a minimum heat production which was proportional to a power of the body weight rather than to the body surface. Galvão has also analyzed the data reported by American authors and has shown that, for Americans living in cold climates, the basal heat production is proportional to $W^{0.69}$ for lean men and to $W^{0.67}$ for well proportioned subjects. The weight, at these powers, nearly represented the body surface area of the American subjects as calculated by the du Bois normogram. In other words, Galvão suggests that the basal metabolic rate is proportional to the surface area in cold climates but not in warm ones. The data given in this paper support Galvão's views but there are other reports in the literature which do not conform to his suggestion.

Thus Mason (4) has measured the basal metabolism of 34 European women living in Madras (S. India). We have analyzed her figures, and the following equations, relating basal calories per hour with body weight or body surface, have been derived:

Total group (34 subjects)

Basal calories $= 4.975\ W^{0.406}$ ($\sigma b = 0.108$)
Basal calories $= 48.49\ S^{0.082}$

Lean women (24 subjects)

Basal calories $= 9.594\ W^{0.416}$ ($\sigma b = 0.184$)
Basal calories $= 45.19\ S^{0.061}$

Well proportioned women (10 subjects)

Basal calories $= 5.010\ W^{0.672}$ ($\sigma b = 0.267$)
Basal calories $= 50.17\ S^{0.096}$

(σb = standard deviation of exponent W)

For these subjects the basal heat production would seem to be more dependent upon the weight than the surface area but the powers of the weight

are different from those reported here for Ceylonese and from those given by Galvão for Brazilians. The climate of Madras is somewhat similar to that of Colombo (Madras has a mean annual temperature of 82.2° F. and a mean relative humidity of 72%), so that it may be that these results from European women represent the effect of acclimatization upon an organism previously adapted to a colder climate, where heat production is a function of the surface area. If this be the sole explanation then we should expect people native to Madras to have a basal heat production which is related to body weight in a manner somewhat similar to that already discovered for other Tropical people.

Mason and Benedict (5) have measured the basal metabolism of South Indian women living in Madras. Examination of their data gives the following relationships:

Total group (54 subjects)

$$\text{Basal calories} = 8.204\ W^{0.439}\ (\sigma b = 0.089)$$
$$\text{Basal calories} = 42.36\ S^{0.052}$$

Lean women (40 subjects)	*Well proportioned women (14 subjects)*
Basal calories $= 7.773\ W^{0.453}$ ($\sigma b = 0.115$)	Basal calories $= 12.29\ W^{0.339}$ ($\sigma b = 0.134$)
Basal calories $= 41.69\ S^{0.076}$	Basal calories $= 45.02\ S^{0.065}$

These equations are somewhat similar to those derived for European women in Madras but are unlike those obtained for Ceylonese and Brazilians. It is difficult to envisage South Indian women having markedly different metabolically active weights from their relatively near neighbors in Ceylon, especially when the latter appear to behave similarly to the residents in distant Brazil. Full discussion of possible explanations of the differences must be left until the completion of further work on the relative importance of the many factors involved in the determination of the rate of basal heat production.

In any event the figures given here for the basal heat production of Ceylonese are lower than those usually accepted for occidental people. It is generally agreed that people living in warm climates have lower basal metabolic rates than those in cooler regions (4, 6, 7); thus, for example, Mason and Benedict (5) reported a mean basal heat production of about 44 calories/hour/person for their group of South Indian women. There may be racial factors involved here (5) especially when it is remembered that Chinese and Japanese women living in the United States are reported to have a low metabolism (8), while Jamaicans are said to have basal metabolic rates similar to North Americans (9). Climate, however, is also important, since Europeans living in the Tropics also have a low metabolism (4, 10, 11).

Whatever the underlying cause, these low basal rates of metabolism in the Tropics are important in defining the calorie requirements of the people living in these regions. One method of computing these requirements is to sum the daily energy needs for basal metabolism, work, minor activities and growth.

Using the regression equations derived above (table 1) for basal calories and weight and the average weight figures obtained from a survey of 10,000 healthy Ceylonese subjects (12), we can calculate the average basal calorie needs (table 3).

These figures do not allow for individual differences in physique but are probably sufficiently accurate for groups of people.

TABLE 1

a) Relationship between basal heat production,[1] and body weight[2] for groups of Ceylonese males and females

SEX	AGE IN YR.	$C = a, W^b$	σ_{b_1}	r_1
Male	10	$C = 3.199\ W^{0.780}$	0.0073	0.9985
	14	$C = 2.844\ W^{0.780}$	0.0164	0.9949
	18	$C = 2.234\ W^{0.798}$	0.0226	0.9897
	21–25	$C = 2.323\ W^{0.776}$	0.0276	0.9710
Female	10	$C = 3.062\ W^{0.786}$	0.0290	0.9932
	14	$C = 2.240\ W^{0.820}$	0.0743	0.9171
	18	$C = 2.265\ W^{0.769}$	0.0563	0.9432
	21–25	$C = 2.274\ W^{0.791}$	0.0268	0.9865

b) Relationship between basal heat production[1] and surface[3] for groups of Ceylonese males and females

SEX	AGE IN YR.	$C = a, S^b$	σ_{b_2}	r_2
Male	10	$C = 33.45\ S^{1.272}$	0.111	0.9218
	14	$C = 37.69\ S^{0.834}$	0.141	0.7778
	18	$C = 31.33\ S^{1.176}$	0.131	0.8819
	21–25	$C = 26.68\ S^{1.140}$	0.095	0.9119
Female	10	$C = 31.80\ S^{1.167}$	0.101	0.9234
	14	$C = 32.94\ S^{1.307}$	0.173	0.8449
	18	$C = 28.11\ S^{1.344}$	0.142	0.8922
	21–25	$C = 31.17\ S^{1.141}$	0.021	0.8759

σ_{b_1} = Standard deviation of regression coefficient b_1.
σ_{b_2} = Standard deviation of regression coefficient b_2.
r_1 = Correlation coefficient between log W and log C.
r_2 = Correlation coefficient between log S and log C.
[1] C: Expressed in cal/hr. [2] W: Expressed in kg. [3] S: Expressed in m^2.

It is always difficult to decide what figures should be taken to represent the average work of an adult man. As Keys (13) has indicated, it is not enough to define the energy requirement for a given job by the measurement of energy expenditure during what is conceived to be the customary activity. Thus, for example, a stenographer usually does more than just sit and type while, on the other hand, a painter is not vigorously painting throughout the whole of his work period. Estimates of the energy expenditure required for various oc-

cupations can only, therefore, be approximations to reality. The Technical Commission of the League of Nations (14) recommended 75 to 150 calories per hour of work as the supplement for the muscular activity of a moderately active man and, on this basis, it is usual to assume a work output of about 1000 calories a day in computing the requirements for Western people.

The type of work usually performed in the Tropics is dissimilar from that done in Western countries. In general, it is not as heavy. Our physical fitness surveys have indicated that the Ceylonese has neither the physique nor the muscular development for such arduous work as the man in temperate climates and his strength is less (15). In addition, the tempo of existence is

TABLE 2. RELATIONSHIP BETWEEN HEAT PRODUCTION[1] AND BODY WEIGHT[2] FOR GROUPS OF LEAN AND WELL PROPORTIONED CEYLONESE MALES AND FEMALES

AGE IN YR.	SEX	PHYSIQUE	$C = a\,W^b$	σ_b	r
10	Male	Lean	$C = 2.972\ W^{0.801}$	0.0227	0.9963
		Well proportioned	$C = 3.214\ W^{0.779}$	0.0168	0.9969
	Female	Lean	$C = 2.825\ W^{0.810}$	0.0021	0.9962
		Well proportioned	$C = 3.420\ W^{0.781}$	0.0046	0.9896
18	Female	Lean	$C = 1.687\ W^{0.853}$	0.2504	0.8116
		Well proportioned	$C = 2.128\ W^{0.783}$	0.223	0.9939
21–25	Male	Lean	$C = 2.051\ W^{0.807}$		
		Well proportioned	$C = 2.612\ W^{0.743}$	0.1136	

σ_b = Standard deviation of regression coefficient b.
r = Correlation coefficient be given log W and log C.
[1] C: Expressed in cal/hr. [2] W: Expressed in kg.

slower in hot climates so that, during working hours, the rate of working is less that that usually found in colder countries. Further, the average weight of an adult, Ceylonese male is about 50 kg. and he is going to require less energy to move himself about than is the heavier (70 kg.) man in temperate climates. For all these reasons the energy needs of the Ceylonese, above his basal requirements, are going to be less than those of the European or the American, and these needs would probably be equivalent to an energy output of 750 calories a day (12). With a work efficiency as low as 20 per cent this would be sufficient for the performance of about 750,000 kilogram meters of external work.

Furthermore, in relaxing Tropical environments, activity tends to be less during the non-working periods of the day so that the leisure hours of the Ceylonese are spent chiefly in sitting.

These considerations would indicate, therefore, the following energy requirements for an average adult working man in Ceylon:

8 hours sleep (basal metabolism)	385 calories
8 hours awake (basal metabolism plus 30%)	500 calories
8 hours work (basal metabolism plus 750 calories)	1135 calories
Total	2020 calories

Allowing the usual 10 per cent loss for incomplete digestion and absorption, this corresponds to the purchase of food equivalent to 2200 calories per day. For hard work, the work allowance would probably have to be doubled and this would give a requirement of about 2800 calories as food.

The requirements of a woman will be less. It is usual to estimate a woman's activity as light work, requiring roughly two-thirds the energy of the moderate work of a man. The Ceylonese woman in the village has a work output that must approach that of the man and so, allowing for the smaller average weight of woman, 600 calories per day may be allowed for this. On this basis, we arrive at the following energy requirements of the average Ceylonese woman:

8 hours sleep	746 calories
8 hours awake	450 calories
8 hours work	946 calories
Total	1742 calories

This would correspond to purchased food equivalent to 1900 calories per day.

It is more difficult to compute the energy needs of children. The growing child is gaining weight and so excess energy must be taken into the body for this purpose. The rate of growth of Ceylonese children is less than that of Western races, e.g. 2.5 kg. per year between 10 and 14 years for males and 3 kg. for females; between 14 and 18 years, 3.5 kg. per year for males and 1.75 kg. for females and, between 18 and 21 years, an increase of 0.5 kg. for the males. These weight increases are roughly equivalent to storing in the body the following calorie contents per month:

AGE	MALE	FEMALE
10 to 14 years	500	600
14 to 18 years	700	350
18 to 21 years	100	

Children are always active; this is nature's method of ensuring healthy muscular and nervous development. This activity tends to be less in the relaxing atmosphere of the Tropics and it is also influenced by food intake, being less with a smaller consumption of food. The Technical Commission of the League of Nations (14) has suggested that, for boys from 11 to 15 years and

and girls from 5 to 15 years, this muscular activity can be considered to be equivalent to light work, and, for boys from 11 to 15 years, as moderate work. We have attempted to estimate, by the Douglas-bag technique, the rate of metabolism of healthy Ceylonese boys, aged 10 years and 14 years, while playing, and we have already given the regression equations relating the body weight to the energy output. The play represented only little more than alternate bursts of running and walking but it was hoped that it would give some indication of the energy expenditure of Ceylonese boys during play. Calculating, by these equations, the energy spent in play by the average boy and taking these in conjunction with the estimated basal metabolic rates given in table 3, and also allowing for the length of time spent in sleeping and at

TABLE 3. AVERAGE BASAL METABOLISM RATES FOR CEYLONESE OF VARIOUS AGES

AGE IN YR.	SEX	AV. WEIGHT	AV. BASAL METABOLIC RATE
		kg.	*cal/hr.*
10	Male	24.0	38.2
	Female	23.3	36.5
14	Male	33.7	44.2
	Female	36.6	42.9
18	Male	47.3	48.5
	Female	40.3	38.9
21–25	Male	49.6	48.1
	Female	43.8	43.2

school or in minor activities (these are average times obtained from our subjects), the energy requirements of these Ceylonese boys can be computed as

Boys aged 10 years:	
12 hours sleep (basal metabolism)	458 calories
6 hours school and minor activities (basal metabolism plus 30%)	298 calories
6 hours 'play' (basal metabolism plus 306 calories)	535 calories
Total	1291 calories
Boys aged 14 years:	
10 hours sleep	442 calories
7 hours school and minor activities	402 calories
7 hours 'play'	817 calories
Total	1661 calories

We have made no estimations of the energy output of Ceylonese girls at play but it seems reasonable to assume that an allowance for play similar to

that for the boys would not be too little and may be too generous (at least at 14 years). Such allowances would make the daily energy requirements of Ceylonese girls, 1240 calories at 10 years and 1670 calories at 14 years.

These theoretical deductions from observed metabolic rates for Ceylonese give daily calorie requirements which are lower than any previously recommended (table 4). It is pertinent to ask, therefore, whether these suggested net daily energy requirements correspond to the observed calorie intakes of Ceylonese subjects.

Most nutrition and dietary surveys in Ceylon have been done on the 'family' basis and the calculations of the energy intake per adult have been made by the use of man-value scales (16–18). The actual figures obtained have been partly dependent, therefore, upon the scale used and, in addition, these scales have invariably been constructed from data obtained from Western

TABLE 4. COMPARISON OF SUGGESTED CALORIE REQUIREMENTS OF CEYLONESE WITH PREVIOUSLY SUGGESTED SCALES OF CALORIE REQUIREMENTS

AGE	SEX	LEAGUE OF NATIONS (27)	NATIONAL RESEARCH COUNCIL (28)	SOUTHERN INDIA (BIGWOOD, 29)	JAPAN (BIGWOOD, 29)	PRESENT VALUES
Adult	Male	3000	3000	2600	2400	2020
	Female	2400	2500	2080	1920	1740
14 years	Male	2400	3200	2080	1920	1660
	Female	2400	2800	2080	1920	1672
10 years	Male	1920	2500	1820	1680	1290
	Female	1920	2500	1820	1440	1240

people. Studies of individual Ceylonese children's diets, of the diets consumed by individual European subjects living in Ceylon and of the diets of individual Ceylonese medical students have, however, been reported (19, 20). All the subjects studied were apparently healthy on clinical examination, they gave good medical histories, were normally active and belonged to the middle classes of Ceylon, so that presumably they could afford to buy an adequate diet. The group of medical students was under constant observation during metabolism experiments for a period of over 3 months (21) and their weight remained constant during this time, which indicates a balanced calorie intake.

The mean daily calorie intake for the group of Europeans was found to be 2770 ± 188 calories for the men and 1910 ± 95 calories for the women. These values are about 90 per cent of those reported by Widdowson (22) and Widdowson and McCance (23) for middle-class men and women living in England and they do agree with the lower metabolic rates which have been observed for Europeans living in the Tropics. The male, adult Ceylonese medi-

cal students had a mean net daily energy intake of 2025 calories (cf. 2020 calories as our calculated requirement). The net mean calorie intakes for Ceylonese boys aged 10 years was found to be 1128 ± 37 calories per day (calculated requirement 1290 calories) and for boys aged 14 years it was 1623 ± 41 calories per day (requirement 1670 calories). These figures indicate, except at the age of 10 years, a remarkably close agreement between observed intakes and calculated requirements.

It can be objected that we are here comparing 'intakes' with 'requirements' but it has been reported that, if people are deprived of some normal source of calories, then appetite compels them to make good this loss by turning to some other source of supply (24, 25). In other words, for healthy people where there are no restrictions on food supplies, calorie intake is a fair measure of calorie requirement.

A further objection may be that we are dealing here with subjects who are much smaller and lighter than the average Occidental and that increased nourishment during the years of growth would improve their physique. In addition the observed low metabolic rates may also be an expression of sub-optimal nourishment. This may be true, but it must be emphasized that we are reporting here results from middle-class Ceylonese and that the great majority of the population have even lower calorie intakes (17, 18). The initial problem is to give the poorer classes a diet which would give them the physique and the health of the middle-classes.

It must be further emphasized that the suggested requirements are only average values, which may be useful when comparing or recommending diets for communities or groups of people; it is doubtful whether they have much value when applied to individuals. Thus, for our groups of men, women and children, the daily calorie intake showed a wide variation between subjects, and other individual dietary studies have given similar results (22, 23, 26). Possible reasons for this have been discussed elsewhere but it does seem that each individual has his or her own characteristic calorie intake and that the factors determining this have still to be defined (19, 20, 27).

Not only does the basal heat production vary from subject to subject, but the apparent energy expenditure on work and the every-day activities of life varies widely between individuals. This is well illustrated by our group of 12 male medical students (*numbers 1* to *12* inclusive of table 6). These students lived in the same hostel and their duties and other activities were very similar. They were under continuous observation, during mineral metabolism experiments, for at least 12 weeks and, on five separate occasions during this period, their individual daily food was weighed for 7 consecutive days. This weighing has enabled us to estimate their average net daily calorie intakes and, in table 5, their intakes are compared with their measured basal heat production. Subtracting the basal heat production from the estimated calorie intakes gives

an estimate of the daily calories used by each individual for his work and daily minor activities. (All the subjects maintained a constant body weight during the period of the experiment.) These excess daily calories vary widely from individual to individual and bear *no obvious relationship* to body weight. Presumably the efficiencies of digestion, absorption, and utilization of food, the specific dynamic action of food and the mechanical efficiency of muscular effort all may vary between individuals and so account for the different calorie needs of these subjects.

TABLE 5. MEASURED BASAL HEAT PRODUCTIONS AND CALCULATED CALORIFIC VALUES OF FOOD INTAKE OF 12 CEYLONESE MEDICAL STUDENTS

SUBJECT NO.	BASAL HEAT PRODUCTION	AV. NET CALORIFIC VALUE OF FOOD	CALORIES IN EXCESS OF BASAL	SUBJECT NO.	BASAL HEAT PRODUCTION	AV. NET CALORIFIC VALUE OF FOOD	CALORIES IN EXCESS OF BASAL
	cal/day	*intake/day*			*cal/day*	*intake/day*	
1	1233	2006	771	*7*	1053	2313	1260
2	1248	2229	981	*8*	1248	1834	584
3	1563	2161	598	*9*	1308	1942	634
4	1374	2115	741	*10*	1380	2049	769
5	1182	1995	813	*11*	1425	1835	410
6	1185	1806	621	*12*	840	2017	1177

SUMMARY

The basal heat production of 225 Ceylonese subjects, male and female and of various ages, has been determined.

It would seem that, for both sexes and at the various ages, the rate of energy production of Ceylonese while resting and fasting can be represented by the equation,

$$\text{Calories/hour} = a\,W^{0.79},$$

this energy production being more closely related to a power of the body weight than to the body surface area. The heat production per unit of metabolically active weight is greater for well proportioned people than for the lean. The energy produced, surplus to basal, by Ceylonese boys during play was proportional to the body weight.

On the basis of these figures, the calorie requirements of Ceylonese have been tentatively computed and those requirements have been compared with the net daily calorie intakes, estimated from measurements of the food intake. A remarkably close agreement between the observed intakes and calculated requirements was obtained.

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Effect of Skin Temperature on Salt Concentration of Sweat

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VARIATIONS IN THE CHLORIDE concentration found in the sweat of men range from 5 mEq/l. reported by Conn, Johnson and Louis (1) in subjects acclimatized to heat, to values above 100 mEq/l. found in some individuals by Robinson, Dill, Wilson and Nielsen (2), Johnson, Pitts and Consolazio (3) and Ladell (4). These variations are not all related to individual variations since sweat collected at different times from the same individual may show different concentrations. Mickelsen and Keys (5), Ladell (6) and Kuno (7) have found that sweat collected from different skin areas of the same man may vary in salt content. Some authors have ascribed the variations in the same individual to acclimatization to a hot climate with accompanying changes in activity of the adrenal cortex, others to changes in salt balance of the individual, and still others to changes in skin and rectal temperature and to the rate at which the sweat is secreted. Johnson, Pitts and Consolazio (3) give some evidence that the lowering of sweat chloride during the days of acclimatization of men to heat may be due to the lowering of skin and rectal temperature as temperature regulation improves. In order to understand the causes and mechanisms of these variations, experiments are needed to test separately the effects of the different factors concerned. In this study we planned to determine if possible the direct effect of temperature of the sweat glands on the salt concentration of the sweat being secreted.

PROCEDURE

Young men in good physical condition were used as subjects in this study. Four of the subjects were studied in varying degrees of acclimatization to heat. The experiments were of 2 to 6 hours duration and were carried out in an air-conditioned room in which air temperature and humidity were held constant during each exposure. The men walked on a motor-driven treadmill at 5.6 km/hr. up a 2.5 per cent grade during the exposures. Sweat for analysis was collected from the men's hands and forearms in elbow-length rubber gloves.

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A tube was fitted into the small finger of each glove so that sweat samples could be drawn at any time without removing the glove. The men's hands and arms were thoroughly washed in distilled water and dried with clean gauze before donning the gloves. Cotton gauze, previously washed with distilled water, was wrapped around the arm and mouth of each glove to prevent sweat from the upper arm from running into it. In order to study the effects of local variations of skin temperature on the volume and composition of the sweat secreted by the hands and forearms, each subject's two gloved hands were maintained simultaneously at different temperatures and the sweat secreted into each glove was collected every half hour. For convenience, the sweat secreted by hand and forearm and collected in the gloves will be called the hand sweat throughout the remainder of this paper. In the environments used in this study the working subject's hands could be maintained steadily between 36° and 37°C. by covering the rubber gloves with wet cloths. Hand temperatures were maintained at any desired level between 20° and 35°C. or above 37°C. by submerging the gloved hand and forearm in water at appropriate temperatures. High hand temperatures were maintained in a few cases by simply exposing the gloved hand to the environment without a bath or wet cloth. Each subject had his left hand cooled in some experiments and his right hand cooled in others. During all exposures the men kept their weights constant by drinking measured quantities of water at frequent intervals. The drinking water was kept at a temperature between 35° and 36°C. Skin temperature was measured at 15-minute intervals by thermocouples held in place by elastic bands at the following locations—knee, chest, shoulder, hip and radial aspects of the first phalanges of both forefingers. Rectal temperature was measured every half hour by clinical thermometer. Total hourly rates of sweating were calculated from the nude weights of the men taken immediately before starting and at the end of each hour of the experiment, taking into account their water intake and urine output, if any was voided, during the experiment. The subjects stopped walking for 5 minutes at the end of each hour for the weighings. Chloride in sweat was determined by the method of Schales and Schales (8) and sodium by that of Butler and Tuthill (9).

RESULTS

Table 1 gives the concentrations of chloride in sweat collected from the hands and forearms of 4 subjects in experiments in which one gloved hand of each subject was kept between 35.7° and 37.1°C. while the other was either cooled or was warmed to an even higher temperature. In 30 of the 31 experiments in which one hand was at least 1.5°C. warmer than the other, the warm hand secreted sweat with a higher concentration of chloride than the cooler hand. With the one exception noted, this local effect of hand temperature on chloride in the sweat was in the same direction regardless of variations in the

TABLE 1. RESPONSES OF MEN TO WORK (M.R. 190 CAL/M²/HR.) IN SEVERE HEAT[1]

DATE	AIR, D.B.	TEMP., W.B.	RECTAL, FINAL	SKIN, AV.	SWEAT, TOTAL	COOL HAND			WARM HAND		
						temp.	sweat	Cl	temp.	sweat	Cl
	°C.	°C.	°C.	°C.	kg/hr.	°C.	cc/hr.	mEq/l.	°C.	cc/hr.	mEq/l.
M.H. (2 hrs. work)											
2/9	50.3	31.5	38.1	35.1	1.27	27.8	22.0	30.6	35.9	12.5	44.2
2/12	50.5	32.5	38.0	36.5	1.19	28.8	19.0	21.9	36.7	13.0	38.5
2/13	50.7	32.6	38.0	36.4	1.13	22.4	5.0	14.3	37.1	10.5	35.5
5/3	50.0	31.0	38.0	36.1	1.26	36.3	28.0	34.2	36.5	28.5	34.1
5/4	49.2	31.2	38.0	34.8	1.39	29.6	36.0	23.0	36.8	46.0	34.5
5/5	50.0	30.9	38.0	35.8	1.41	34.3	62.0	26.1	35.9	58.0	43.2
5/6	49.6	30.4	38.0	35.7	1.56	36.7	56.0	40.5	38.8	52.0	42.8
5/7	44.5	28.0	37.8	35.4	1.05	34.7	34.0	19.5	36.2	36.5	21.5
5/10	45.0	29.0	38.0	36.0	1.26	34.2	36.0	20.7	36.3	40.5	28.3
5/11	44.6	29.7	37.9	35.6	1.10	30.2	25.0	11.5	36.2	28.0	25.2
5/12	44.2	27.8	37.8	35.1	1.10	35.9	35.0	30.9	38.7	48.0	34.9
5/14	45.3	27.9	37.9	35.2	0.99	25.6	20.0	10.0	36.4	51.5	26.6
R.B. (2 hrs. work)											
2/9	50.3	31.5	38.5	36.2	1.36	27.9	18.0	50.0	36.7	16.0	58.5
2/12	50.5	32.5	38.3	36.2	1.17	29.0	32.0	48.8	36.7	8.0	60.5
2/13	50.7	32.6	38.3	35.6	1.44	19.7	10.0	31.7	36.5	10.0	43.9
5/3	50.0	31.0	38.2	36.0	1.41	36.0	32.5	64.9	36.4	26.5	76.8
5/4	49.2	31.2	38.1	34.3	1.55	29.5	32.0	44.8	36.1	26.0	60.6
5/5	50.0	30.9	38.0	35.2	1.45	34.1	35.5	45.5	36.2	29.5	50.4
5/6	49.6	30.4	38.1	35.9	1.75	36.5	38.5	58.1	38.8	23.5	47.2
5/7	44.5	28.0	38.0	35.2	1.25	35.0	18.5	22.4	35.7	16.0	28.8
5/10	45.0	29.0	38.0	35.9	1.35	34.1	25.0	41.9	36.4	25.0	42.0
5/11	44.6	29.7	37.9	35.4	1.17	29.8	14.0	16.3	36.0	13.0	34.7
5/12	44.2	27.8	37.9	35.2	1.21	35.9	15.5	35.1	38.6	9.5	41.1
5/14	45.3	27.9	38.1	35.1	1.03	24.9	20.0	14.7	36.0	22.0	28.4
R.S. (1 hr. work, 1 hr. rest, 2 hrs. work)											
5/16	51.0	31.2	38.4		1.33	28.0	21.0	16.5	36.8	12.0	18.3
5/30	51.7	27.4	38.1		1.27	22.2	35.5	33.0	36.2	51.0	45.9
5/31	50.1	28.2	38.2		1.44	31.0	51.0	30.9	35.7	59.0	43.1
6/1	49.6	29.5	39.2	36.2	1.44	36.7	20.5	19.9	38.8	24.0	21.6
R.M. (1 hr. work, 1 hr. rest, 2 hrs. work)											
5/16	51.0	31.2	38.6		1.26	25.5	10.0	8.1	36.5	21.0	12.1
5/30	50.7	27.4	38.0		1.25	20.5	24.5	14.5	36.9	34.5	31.2
5/31	50.1	28.2	38.0		1.51	30.4	60.0	18.6	36.4	70.0	28.7
6/1	49.6	29.5	38.6	36.3	1.51	37.2	58.0	16.0	38.6	46.0	16.4

[1] The temperatures of their hands and forearms were controlled and hourly sweat samples for analysis were collected simultaneously from both hands in elbow-length rubber gloves during work periods.

general level of sweat chloride which might be due to acclimatization, to the rate at which the sweat was secreted, or to possible other factors.

There were reductions of chloride in the sweat from day to day with repeated exposures of the men to heat and yet the differences between the sweat chloride of the 2 hands maintained at different temperatures in the same exposure were present at all levels of acclimatization. This may be seen in the data from *subjects R.B.* and *M.H.* where reductions of sweat chloride related to acclimatization were moderate because they were sweating only 2 to 3 kg/day in 2 hours of work in the heat (fig. 1). It is also shown in *subjects R.S.* and *R.M.* in whom acclimatization was more complete because they were sweating 5 to 6 kg/day in 4-hour exposures (table 1). The last 2 men had just completed 7 daily exposures on May 16 and the chloride concentrations in their sweat were low. They had 14 days of rest from the heat with unrestricted diet before starting the experiments on May 30; as a result their sweat chlorides were again high on the starting day but underwent rapid reductions in the following 2 days. The characteristic effect of differences in hand temperature on sweat chloride during a single exposure occurred in all of these experiments.

The data in table 1 show only small variations of the men's rectal temperatures from one experiment to another and in this range the variations of sweat chloride due to differences in hand temperature during a given exposure were independent of rectal temperature, i.e. a high hand temperature raised the sweat chloride regardless of the height of the rectal temperature. This indicates that the observed temperature effect is directly on the sweat glands and not through nervous or hormonal mechanisms. The small variations of rectal temperature of each individual which occurred from day to day in these experiments were dependent upon variations of the heat stress and of the subject's state of acclimatization and salt balance. Cooling one hand and forearm to 25°C. significantly lowered the overall heat stress under otherwise constant conditions. A salt deficit produced by losing more salt in the sweat for 2 or 3 days than is being ingested results in elevated rectal temperature by men working in the heat (10). The relative constancy of rectal temperature in these experiments was dependent upon the fact that all 4 men were partially acclimatized in so far as heat regulation was concerned as a result of exposures to similar stresses 2 to 4 weeks before these experiments were begun. Robinson *et al.* (11) have found that men retain their ability to regulate body temperature under heat stress for several weeks after exposures cease. On the other hand the reduction of sweat chloride occurring with acclimatization to heat may be lost in 4 to 8 days following the last exposure to heat.

Dill *et al.* (12) found a positive relation between sweat chloride concentration of men and the rate at which the sweat was secreted. Our data in table 1 indicate that the rate of sweat secretion by hand and forearm was subordinate to hand temperature as a factor in determining the concentration of chloride in the sweat. In *R.B.* hand temperatures of 36° to 38.8°C. reduced the rate of sweating by hand and forearm to values below those observed in

the cooler hand. A similar reduction of sweating by the warm hand was observed in from one-fourth to one-third of the experiments on the other 3 subjects. However, the differences in the concentration of chloride in the sweat due to hand temperature were not affected by these variations in the rate of sweating in the hand. In 15 experiments on all 4 subjects the cool hand and forearm were found to sweat faster than the warm hand and forearm, and in 14 of these 15 experiments the chloride concentration was lower in the cool hand. In 14 experiments the warm hand secreted more rapidly than the cool hand and yet the increases in chloride concentration in sweat from the warm hand were no greater than in the experiments in which the warm hand had secreted less rapidly than the cooler hand. The high rates of sweating maintained in the cooled hands of these subjects are dependent upon the intense general stimulus for sweating provided by the extreme heat and work stress. The depression of sweating by high skin temperature under these conditions has been previously reported and discussed by Robinson and Gerking (13).

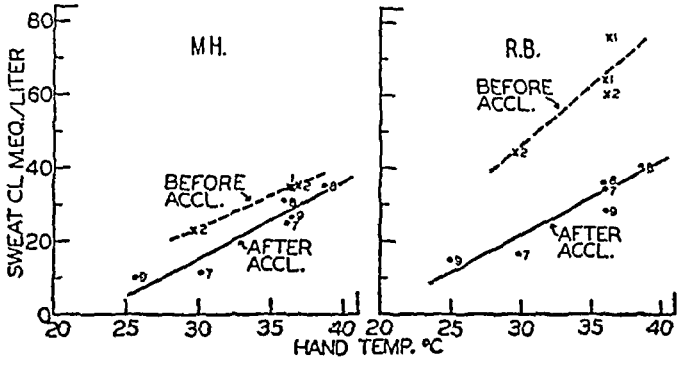

Fig. 1. RELATION OF HAND TEMPERATURE to the chloride concentration of sweat secreted from the hands of men on days 1 and 2 before acclimatization to heat, as compared with values obtained after 7 to 9 days of acclimatization. The temperatures of each subject's 2 hands were controlled simultaneously at different levels during each exposure. See table 1 for conditions of work and environment during the experiments from May 3 to May 12.

As a further test of the effect of local temperature on the concentration of salt in the sweat, two 3-hour experiments were run on *subjects M.H.* and *R.B.* in which one gloved hand was maintained at 36°C. throughout the experiment while the opposite hand was kept at 39.5°C. during the first hour, changed to 28°C. in the second hour and finally raised to 36°C. in the third hour. Samples of sweat were collected each half-hour. The effects of these variations of temperature on salt content of sweat are given in figure 2. In the hand whose temperature was varied there was a marked reduction of chloride concentration in the sweat during the hour of cooling and then a gradual rise in the third hour when the temperature was raised again. No such changes occurred in the hand maintained at a constant temperature.

As an additional test of the consistency of the temperature effect on the salt concentration in sweat, experiments of 4 to 6 hours duration were carried out on 4 partially acclimatized men working at the standard rate in humid heat (dry bulb temperature 34.5°C., wet bulb 33.5°C.). The skin temperature of one of each subject's gloved hands was kept at approximately 37°C. while

the opposite hand was cooled throughout each exposure and samples of sweat from hands and forearms were taken each hour. The men's average skin temperature remained practically constant at about 36°C. throughout the exposures. Their average rectal temperature rose from 38.3°C. in the second hour to 38.6°C. in the last hour. Their total rates of sweating in the first hour averaged 1.33 kg. and had declined to an average of 0.4 kg. in the last hour of work. The detailed results of the observations on the temperature and sweat secretion of their hands and forearms are given in table 2, and average values are given in figure 3. In all 4 subjects the concentrations of both sodium and chloride in the sweat of the warm hand were consistently higher throughout the exposures than corresponding values for the cooler hand. In general sodium was slightly more concentrated than chloride in the sweat. The lower salt concentration of sweat secreted by the cool hand prevailed in all 4 subjects

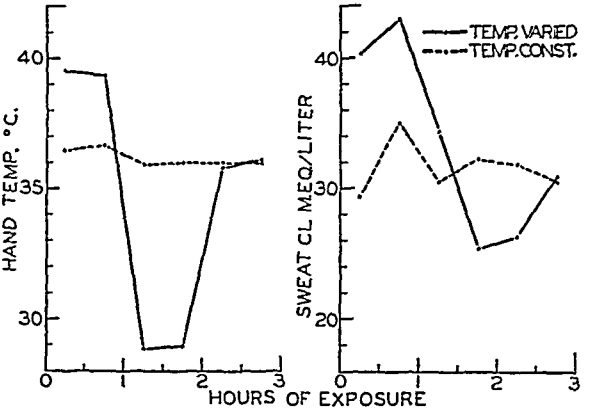

Fig. 2. EFFECT OF CHANGING THE TEMPERATURE of one hand upon the concentration of chloride in sweat being secreted from this hand as compared with values obtained simultaneously from the subject's other hand which was maintained at a constant temperature. Values plotted represent averages of data obtained in experiments on *subjects R.B.* and *M.H.* The men walked on the treadmill (M.R. 190 Cal/m²/hr.) during each exposure (D.B. 45.2; W.B. 28.7°C.).

even though the rate of sweat secretion by the cool hand was consistently and significantly higher after the first hour than the rate observed for the warm hand. This is further evidence that local temperature is a more important factor than the rate of sweat secretion in determining the salt concentration of the sweat. However, it is evident from the data in figure 3 that the general changes in the rate of sweating by a given hand in relation to hours of exposure were accompanied by parallel changes in salt concentration of the sweat: i.e. a decline or increase in sweating with time was generally accompanied by a corresponding decline or increase in the concentration of salt. Although this relationship prevailed it cannot be said that the changes in sweat rate caused the corresponding changes in sweat chloride. As stated above, the men's rectal temperatures tended to rise slightly between the second and last hours of exposure, a change which was in the opposite direction from the changes in sweat chloride during the same time.

It should be emphasized that the data (table 1 and fig. 1) provide evi-

dence that the reduction of sweat chloride from day to day occurring in acclimatization is not necessarily dependent upon a reduction of the skin temperature, the rectal temperature or the rate of sweating of the subject. In fact, with *subjects R.S.* and *R.M.* who were sweating 5 to 6 kg/day, acclimatization from May 30 through June 1 caused daily reductions of sweat chloride from a given hand despite corresponding increases in hand temperature ranging from

TABLE 2. SALT CONCENTRATION IN THE SWEAT OF MEN IN 4- TO 6-HOUR PERIODS OF WORK (M.R. 190 CAL/M²/HR.) PERFORMED IN SEVERE HEAT (D.B. 34.5; W.B. 33.5°C.)[1]

SUBJ.	1ST HOUR		2ND HOUR		3RD HOUR		4TH HOUR		5TH HOUR		6TH HOUR	
	warm hand	cool hand	warm hand	cool hand	warm hand	cool hand	warm hand	cool hand	warm hand	cool hand	warm hand	cool hand
						Hand Temperature, °C.						
J.P.	36.9	29.8	37.0	31.4	37.0	28.9	36.9	27.2	36.9	28.5	37.2	28.5
B.B.	37.2	33.1	36.8	33.7	36.9	33.1	36.5	32.3	36.8	31.9	36.8	31.6
L.G.	36.6	24.8	36.6	30.3	36.5	30.5	37.1	28.6	37.2	28.6	37.1	28.6
W.K.	37.0	26.2	37.2	26.9	37.1	25.6	37.4	26.6				
						Hand Sweat, cc/hr.						
J.P.	89.4	80.0	72.0	98.5	53.7	68.9	43.5	51.4	36.3	40.4	28.1	36.9
B.B.	57.0	58.9	32.0	45.0	23.5	33.3	12.4	20.9	9.1	18.1	8.7	19.3
L.G.	61.2	39.7	37.7	58.7	21.3	43.0	13.9	27.7	9.6	24.6	9.0	24.0
W.K.	49.2	28.3	36.0	46.5	24.8	36.0	17.3	33.0				
						Sweat Chloride, mEq/l.						
J.P.	18.2	13.6	17.6	16.6	16.2	16.0	14.5	13.6	15.3	13.6	15.7	13.6
B.B.	56.4	49.2	51.3	45.6	49.7	41.0	43.6	32.8	37.0	24.1	43.6	29.8
L.G.	49.6	34.8	48.5	47.2	52.3	43.4	48.5	36.0	39.2	28.3	36.0	27.4
W.K.	28.9	19.5	31.0	26.8	35.1	26.5	28.9	25.1				
						Sweat Sodium, mEq/l.						
J.P.	18.6	16.6	18.8	17.5	18.0	16.5	15.0	14.7	16.4	14.1	14.5	14.1
B.B.	57.7	51.1	52.3	47.3	50.9	41.8	49.7	33.3	38.0	24.2	45.0	30.3
L.G.	51.6	44.4	51.2	48.4	52.4	45.1	47.1	34.8	37.8	26.3	36.0	24.0
W.K.	28.8	20.2	29.4	25.9	29.8	24.3	25.4	22.0				

[1] The temperatures of their hands and forearms were controlled and hourly sweat samples for analysis were collected in elbow-length rubber gloves.

22° to 38.8°C. and of rectal temperature from 38.0° to 39.2°C. Table 1 shows that when the daily sweat volume was large, acclimatization was a more dominant factor than either elevated skin temperature or rectal temperature in determining sweat chloride concentration. As pointed out above the data in table 1 and figure 3 show that local temperature of the skin and sweat glands is dominant over the rate of sweating in determining the salt concentration in the sweat.

DISCUSSION

The above data on men working in severe heat provide ample evidence that locally cooling the skin below 36°C. lowers the salt concentration of the sweat being secreted and a higher skin temperature raises the concentration. There are three interesting characteristics and relationships of this response: *1*) The effect appears to be direct and not dependent upon a central or a hormonal control. The evidences for this are: *a*) if the 2 hands and forearms of a man were simultaneously kept at different temperatures, the chloride concentration of sweat collected from the cooler one was significantly lower than from the other, *b*) raising the skin temperature of a single hand and forearm raised its sweat chloride within 30 minutes, while lowering the skin temperature lowered the sweat chloride, and *c*) the effect on sweat chloride was independent of variations in the men's rectal temperature observed during the exposures. *2*) The direct effect of temperature in altering the salt concentration of sweat

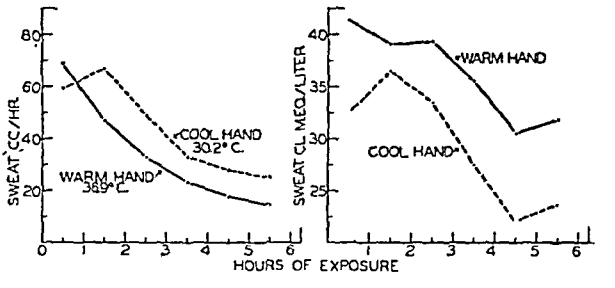

Fig. 3. COMPARISON OF SWEAT collected simultaneously from both hands of men walking on the treadmill (M.R. 190 Cal/m²/hr.) in humid heat (D.B. 34.5°C., W.B. 33.5°C.). The skin temperature of one hand of each man was maintained at an average of 37°C. while the other hand was cooled. The data represent averages of hourly values obtained on *subjects J.P., B.B. and L.G.* who continued the work for 6 hours. See table 2 for individual values.

was found at all stages of acclimatization, and yet the concentrations in both the warm and the cooled hand were reduced progressively by acclimatization. *3*) This effect of temperature was not dependent upon an increased rate of sweating from the region of higher temperature because in a majority of the observations local elevation of the skin temperature of hand and forearm above 36°C. reduced the rate of sweating by the warmed skin area below rates observed simultaneously on the other hand and forearm being held at a lower temperature and yet in 96 per cent of all observations the cooler hand secreted more dilute sweat. On the other hand, changes in the rate of sweating during the course of a single exposure were found to be related directly to changes in the concentration of chloride in the sweat when the hand temperature was held constant.

It must not be concluded from this discussion that the temperature of the sweat glands alone determines the salt concentration of the sweat of any one individual. Rather the data show that at least three factors (skin temperature, rate of sweat secretion and acclimatization) may operate alone or by super-

imposing their effects upon each other. Evidence from the data shows that of the factors concerned acclimatization is dominant over the others under conditions involving the secretion of large volumes of sweat each day.

SUMMARY

Men were exposed to severe work and heat stress in an attempt to determine the effect of varying the temperature of the skin and sweat glands on the salt concentration of sweat collected from the subjects' hands and forearms in elbow-length rubber gloves. When the 2 hands and forearms of each subject were simultaneously kept at different temperatures, the sodium and chloride concentrations of sweat collected from the cooler hand were significantly lower than from the other. The salt concentration of sweat from a single hand was raised or lowered within 30 minutes by a corresponding raising or lowering of the hand temperature. This direct effect of local temperature on sweat chloride was independent of the men's rectal temperatures observed during the exposures, was not dependent upon an increased rate of sweating from the region of higher temperature, and it was found at all stages of acclimatization to heat.

The concentration of salt in hand-sweat was reduced by acclimatization involving the secretion of large volumes of sweat by the men during daily exposures to work in the heat. In two series of experiments in which the men sweated 5 to 6 kg/day, acclimatization produced significant reductions of sweat chloride on the second and third days of exposure even when the rates of sweating, rectal temperature and hand temperature were increased by greater stress.

The authors are greatly indebted to J. L. Pope, Robert Bertholf, Walker Kirkes, Leon Glatt, Richard Shook, Richard Mundy, Max Headley and Robert Burger who served as subjects in these difficult experiments.

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Relation of Maximum Grip Strength to Grip Strength Endurance

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STRENGTH HAS BEEN MEASURED by dynamometers of various types since their introduction by Brigham in 1872 (1). In general, strength has been measured either as contraction (2–4) or breaking strength (5, 6), expressed as pounds or kilograms. Up to the present time the dynamometers employed provide for measuring maximum strength only. If one wishes to gain a complete picture of strength in man, it seems necessary to record not only maximum strength, but also the tension developed by a group of muscles over a period of time.

In order to provide a complete picture of the tension which one is able to develop in a group of muscles, thus providing a means of comparing maximum strength with strength endurance, the dynamometer described in the following discussion was devised. In the investigation herein reported, only grip strength was studied, thus only a grip dynamometer is discussed. It should be added that the principles employed in the grip strength technique are equally applicable to the measurement of the strength of almost any other muscle group.

METHODS AND PROCEDURE

General Description of the Grip Dynamometer. The dynamometer is shown in figure 1. The subject places his hand around the grips *A* and *B* with the little finger against the stop *C*. This insures that the hand will be in the same position on the dynamometer when repeated tests are made. When the subject squeezes, the lower ends of the dynamometer are pulled together, thus causing a small amount of bowing in the region above the fulcrum *D*. The bowing activates a strain gauge (Statham Model G1) *E*. This arrangement is used since the force required to actuate the gauge is much smaller than the grip strength.

The dynamometer is made of tool steel with the dimensions as shown in figure 1. The grips *A* and *B* are made of aluminum and are secured by screws. As described, this dynamometer provides for a full-scale reading of 170 pounds. Other dimensions may be used to give either larger or smaller full-scale readings, but this is sufficiently large to measure the grip strength of the majority of men. A less resistant dynamometer with a full-scale reading of 110 pounds

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was constructed for women. Because of possible variations in the modulus of elasticity, different dynamometers may give somewhat different full-scale readings even though they are made to the same dimensions.

It is necessary to protect the strain gauge against movement beyond its normal limit, which in this instance is 0.0014 in. This limitation of movement is accomplished by inserting between the handles of the dynamometer a block *F*, figure 1, of such thickness that a mechanic's dial indicator placed at *G* reads a displacement of slightly less than the movement limit of the gauge (0.0014 in.), when the handles of the dynamometer are squeezed together. The range of the instrument is then the force required to close the handles of the dynamometer.

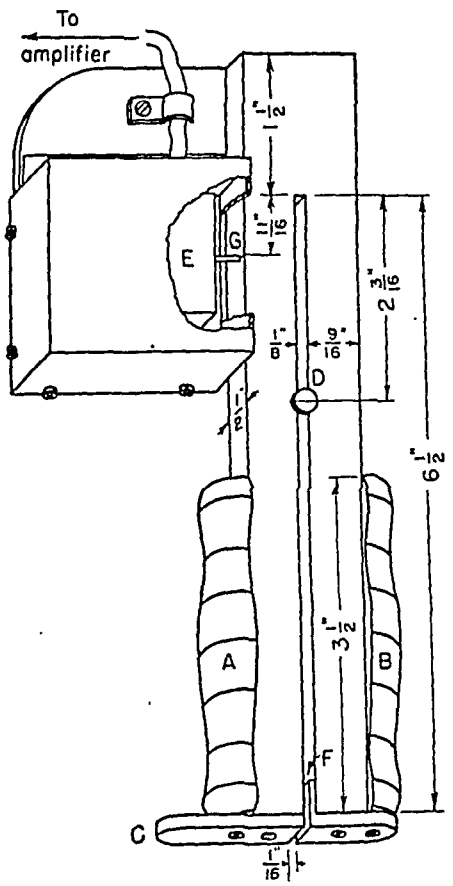

Fig. 1. Grip dynamometer for men.

If the capacity of the dynamometer turns out to be different from that desired, various changes can be made to alter it. *a*) Assuming the strain gauge contact is above the point at which the bulge is greatest, moving the gauge contact *G* up will allow the use of a thinner block at *F* and increase the range. *b*) Increasing the cross-section of the arms of the dynamometer will increase the range; and *c*) changing the position of the fulcrum *D* will change the range.

Strain Gauge. The strain gauge contains a Wheatstone bridge. The 4 resistance elements are stretched wires. When the pin, which contacts the side of the dynamometer at *G* is depressed, 2 wires, in opposite legs of the bridge, are stretched further and the other 2 wires are allowed to shorten. The result is a slight increase in resistance in the first 2 wires and a slight decrease in resistance in the second 2 wires. If the bridge was balanced to begin with, it now is unbalanced. The movement of the pin is so slight that the output voltage is linearly related to the amount of depression of the pin.

Any Statham G1 strain gauge is suitable as far as we know. The model G1-8-130 was selected and found satisfactory. The specifications for this model are: range, 8 oz.; maximum input voltage, 5; nominal resistance, 130 ohms; and maximum output voltage, 13 mv.

Amplifier and Recorder. Obviously, if one is to record the output of the gauge, an amplifier must be employed. The amplifier for the output voltage

of the bridge and the supply for the input voltage are mounted as small units in a single cabinet. They are connected to the strain gauge by a 4-wire shielded cable. The input is 2.5 volts, 60 cycle a.c., supplied by a filament transformer. The a.c. output from the strain gauge is fed into an electronic a.c. amplifier[1], with a characteristic which is linear over most of its range. The output of the amplifier is rectified and operates a 5 ma. d.c. Esterline-Angus recording meter. The meter is operated at a chart speed of 3 inches (4 divisions) per minute. The output signal from the strain gauge is proportional to the input voltage. Thus it was necessary to adjust the input voltage to the gauge and the gain of the amplifier so that the range of the dynamometer corresponds to the full scale deflection of the recorder.

Dynamometer Calibration. If the same force is applied to different points on the grip of the dynamometer different gauge readings will result, due to the variations in the length of the lever arm involved. This requires that calibration force be applied at some uniform point on the dynamometer grip, so as to make calibration values reproducible. In order to calibrate the dynamometer, weights of known quantity are applied to the midpoint of one handle of the dynamometer. This is accomplished by turning the dynamometer on its side in a cradle which always holds the lower handle in the same position, thus preventing variations in the point to which the force is applied. In order to apply the weight to the desired point a $\frac{3}{4}$-inch pipe attached to a fulcrum extends over and rests on the upper grip. Vertical guides prevent lateral displacement of the pipe. A vertical rod through the end of the pipe supports the weights. The distance from the fulcrum of the pipe to the point of suspension of the weights is twice the distance from the fulcrum of the pipe to the midpoint of the handle of the dynamometer. The weight of the lever is counterbalanced so that the force on the gauge is twice the weight applied. A calibration curve (fig. 2) is established by plotting the weights applied against the Esterline-Angus recorder units. The calibration curve is linear except in the lower 10 to 20 per cent of the range. Here it curves off, because of the nonlinearity of the amplifier at such low signals. This, however, is unimportant

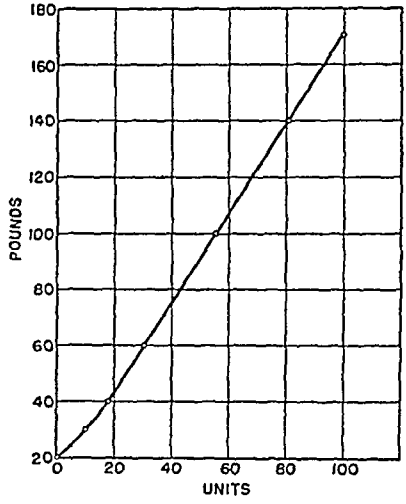

Fig. 2. CALIBRATION CURVE for the grip dynamometer for men.

[1] The amplifier employed was furnished by the Collins Radio Company, Cedar Rapids, Iowa.

since no one has been found with a strength as small as 20 per cent of the range of the dynamometer used.

In this laboratory 2 grip dynamometers are employed, one for women and one for men. The one for women has a full-scale capacity of 110 pounds and the one for men, 170 pounds. It is a simple matter to change dynamometers since it is necessary only to plug the dynamometer into the amplifier and secure it by a lock-nut. The dynamometer described not only provides for the quantitative measure of maximum strength but also for recording the strength for any desired period of time, thus providing a record of strength endurance.

Strength Record. A strength record is shown in figure 3. In this laboratory it is the practice to record maximum strength over a period of one minute. Apparently one minute of maximum effort gives a representative picture of

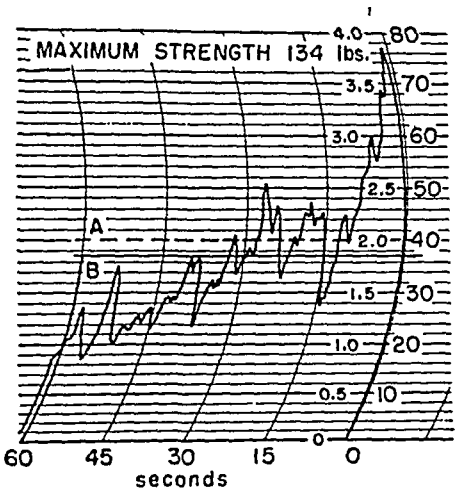

Fig. 3. STRENGTH RECORD for a period of one minute made by the Esterline-Angus recorder. Read from right to left.

what an individual will do, since the output falls off considerably and the subject is well exhausted by the end of this time. In general, all strength records are alike. The records show that maximum strength is quickly attained. From this point there is a gradual but irregular falling off in strength.

Strength Endurance. In this laboratory, strength endurance is defined as the average strength for one minute expressed as pounds.

If the recording meter made a graph in rectangular coordinates the strength endurance index would be found by measuring, with a planimeter, the area under the strength curve, and dividing by the length of a one-minute time interval on the chart. In Esterline-Angus recorders, however, the ordinate (strength) is measured over the arc of a circle instead of a straight line, thus complicating the problem. This requires that allowance be made for this characteristic; the procedure for making the adjustment is as follows:

In the notation of calculus,

$$\bar{S} = \frac{1}{T}\int_{t=0}^{t=T} S(t)\,dt \qquad (1)$$

where $\bar{S}$ = average strength, and T = length of time interval. $S(t)$ represents the curve of strength as a function of time. In order to interpret this integral in terms of the area under the curve, refer to figure 4. The element of area is a parallelogram (Z, fig. 4) whose area is

$$dA = dt \cdot ds \sin \alpha = -R \cos(\beta - \gamma)\, d(\beta - \gamma) dt \qquad (2)$$

For the present, values of ds, $S(t)$, $\bar{S}$, dt, T, and R will be measured in centimeters; and dA and A will be measured in square centimeters.

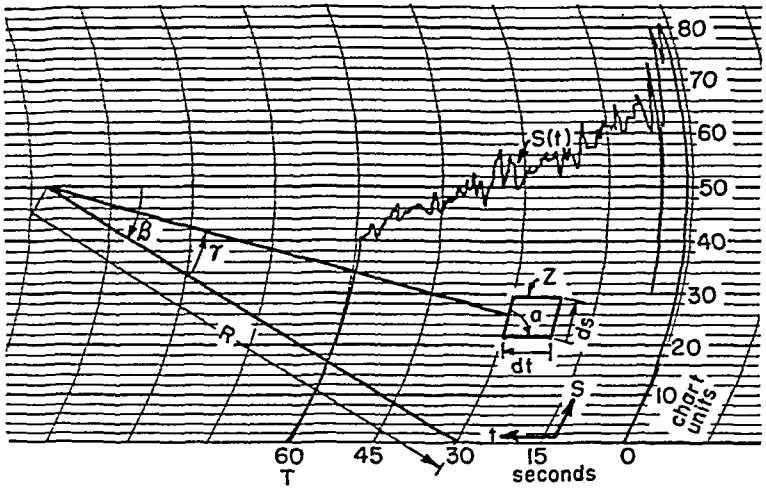

Fig. 4. ELEMENT OF THE AREA used in calculating the relation of average strength for one minute, to the area under the strength curve. Read from right to left.

Integrating *equation 2* gives

$$A = \int_{t=0}^{t=T} S(t) \cdot F(S)\, dt \qquad (3)$$

The curve of $F(S)$ can be calculated from the dimensions of the meter and chart which are used. For the chart used by the authors, $F(S)$ is as shown in figure 5. It is to be noted that the variations in S which are observed in any single strength record result in only small percentage changes in F. This makes it possible to evaluate the integral in *equation 3* with satisfactory accuracy by the following approximation.

The mean value of the chart reading, $\bar{S}$, is estimated by inspection of the chart. The value of $F(\bar{S})$ corresponding to this reading is determined from the graph (fig. 5). Let us call this mean value $\bar{F}$. Then $\bar{F}$ is substituted for $F(S)$ in *equation 3*:

$$A = \int_{t=0}^{t=T} S(t) \cdot \bar{F} \cdot dt$$

Since $\bar{F}$ is constant

$$\frac{A}{\bar{F}} = \int_{t=0}^{t=T} S(t)\, dt$$

Substituting in *equation 1* we get:

$$\bar{S} = A/T\bar{F} \qquad (4)$$

A is measured in square centimeters. If P is the planimeter reading and p is the factor for conversion of planimeter reading to square centimeters, then $A = Pp$. Since the strength endurance index is the average strength for one minute, T is the distance the chart travels in one minute in the recording meter.

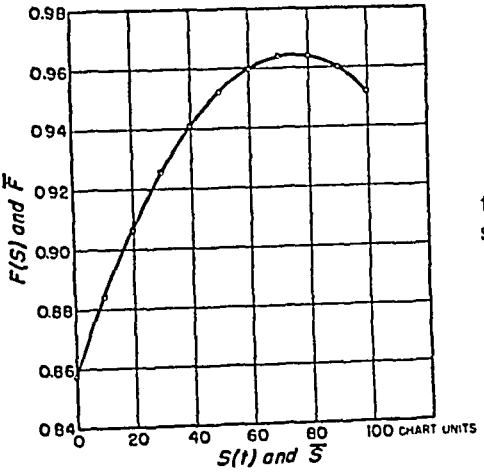

Fig. 5. FACTOR FOR CORRECTION of the area, due to curvilinear coordinates, in the computation of average strength for one minute.

Since it is more convenient to measure $\bar{S}$ in 'chart units' than in centimeters, we divide the right hand member of (4) by the length of one chart unit in centimeters. If the length of this unit is a, then $\bar{S} = Pp/aT\bar{F}$ chart units; or $\bar{S} = (p/aT)P/\bar{F}$ chart units. The quantity (p/aT) must be evaluated for each chart, chart recording speed and planimeter. In the author's case, $p = 16.77$ sq. cm/planimeter unit, $T = 7.59$ cm., and, $a = 0.120$ cm. Hence

$$\bar{S} = 18.41\ (P/\bar{F}). \qquad (5)$$

Formula 5 was used for computing $\bar{S}$ and the strength in pounds corresponding to this number of chart units was obtained from a calibration table constructed from figure 2.

In order to estimate the error involved in the approximation for $F(t)$, the average values of a limited number of charts were determined by dividing the interval T into 12 equal smaller intervals. Each of these intervals was short enough to permit an average for that interval to be estimated by inspection.

The 12 numbers so obtained were then averaged to obtain $\bar{S}$. A comparison of results showed only one case in which the discrepancy between the value of $\bar{S}$ yielded by this method and that yielded by *equation 5* was greater than one chart unit. Thus it seems that *equation 5* yields a value of $\bar{S}$ which is correct to ±1 chart unit. It does not seem worthwhile to try for greater accuracy since the meter reading itself is not more nearly correct than ±1 chart unit.

Calculation of the Strength Endurance Index. The strength endurance index was determined as follows:

1) Estimate the average strength for the duration of the effort by inspection (*A*, fig. 3).

2) Find the value of $(\bar{F})$ from figure 5.

3) Measure the area under the strength curve with a planimeter and record it as planimeter units.

4) Find the average strength, expressed as chart units, by dividing the planimeter reading by $(\bar{F})$, and multiplying this value by 18.41, which is the value of $\bar{S}$ (see calculations).

TABLE 1

	RIGHT HAND (*lbs.*)	LEFT HAND (*lbs.*)
Maximum strength	108 ± 21	95 ± 18
S.E.I.	62 ± 12	55 ± 10
% S.E.I. of M.S.	60 ± 9	58 ± 9

5) Refer to figure 2 to find the pounds equivalent of the average strength expressed as chart units. This is the strength endurance index.

In figure 3, estimated average strength = 40 chart units (*A*); value of $(\bar{F})$ (from fig. 5) = 0.94; area under the curve = 1.91 planimeter units; $1.91 \times 18.41/0.94 = 37$ chart units (*B*, fig. 3); *S.E.I.* = 70 pounds (fig. 2).

Calculation of Maximum Strength. Maximum strength is calculated by finding the highest point on the strength curve, in chart units. Then, by referring to figure 2, the pounds equivalent to this value is secured. In figure 3, the highest point on the curve is 77 chart units which is equivalent to 134 pounds.

Relation of Maximum Strength to Strength Endurance. The dynamometer just described provides a method for gaining information relative to the question of whether the development of maximum strength is accompanied by a development of a proportionate amount of strength endurance. In order to gain the desired information, data were collected from a group of 200 subjects. All those participating in the experiment were normal males ranging in age from 20 to 30 years. A strength record, representing the maximum gripping effort for a period of one minute was made by each subject for both right and left hands. The strength data are summarized in table 1.

In order to find the relationship between maximum strength and strength endurance, the maximum strengths for each subject were correlated with the strength endurance indices. The coefficient of correlation for the right hand was 0.67 and for the left, 0.66. This means that the individual with the stronger grip can maintain a higher level of strength for the period of effort investigated, the result being the same for both hands.

Another question of interest relative to strength is, does the individual who possesses a high maximum strength possess strength endurance which is proportional to his maximum strength? In order to gain information relative to this point, the percentage of the maximum strength maintained for the one-minute period was correlated with the maximum strength. For the right hand, the coefficient of correlation was −0.40 and for the left −0.41. This means that the stronger individual can maintain less of his maximum strength for a one-minute period than the individual who is less strong. This leads to the conclusion that the development of strength endurance is not directly proportional to the development of maximum strength.

SUMMARY AND CONCLUSIONS

A dynamometer for measuring and recording maximum grip strength and strength endurance is described. In order to show the relationship between grip strength and grip strength endurance, data were collected from 200 university men between the ages of 20 and 30 years. The percentage of the maximum grip strength which was maintained for one minute (strength endurance) was correlated with maximum grip strength. The coefficient for the right hand was −0.40 and for the left, −0.41. This suggests that stronger individuals can maintain a smaller proportion of their maximum strength than those with less initial strength. However, a correlation of maximum strength with the strength endurance index gave a coefficient of 0.67 for the right hand, and 0.66 for the left. This indicates that the individuals with the greater maximum strength have a greater strength endurance index.

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Response of Human and Canine Gall Blaader to Cholecystokinin[1]

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THE CLINICAL INTEREST in cholecystokinin (CCK) stems from the possibility that it may serve as a valuable means for ascertaining the evacuatory response of the gall bladder to a standard stimulus. Although the Boyden fatty meal is now widely employed by radiologists for this purpose, several disadvantages are apparent. The meal does not present a standard stimulus in that the rate of emptying of the meal from the stomach is subject to variation. This difficulty is probably enhanced when patients object to the taste or are nauseated by the meal. The latter does not lend itself for the grading of normal and abnormal function on a unitage basis as might be the case with CCK where definite dosages can be injected. Furthermore, it has been the hope of one of us (*A.C.I.*) that CCK might prove to be of value for the diagnosis of biliary dyskinesia (1).

Gall bladder evacuation in response to CCK was first studied in dogs and cats by Ivy and Oldberg (2), who employed a rather crude preparation ('1802'), likewise containing secretin (3). In one series of experiments on dogs, lipiodal was introduced aseptically into the gall bladder after the removal of some bile. From 18 to 24 hours later, the fasted, unanesthetized dogs were injected every 10 minutes for one hour with a dose of CCK concentrate. In 9 of 10 dogs, one-half or more of the lipiodal was evacuated from the gall bladder. Complete emptying of the viscus was not observed at any time.

The investigation was later extended to human subjects by Ivy, Drewyer and Orndoff (4). Five normal subjects and 3 patients with biliary tract symptomatology volunteered for the study. A somewhat improved concentrate of CCK was employed, and visualization of the gall bladder was obtained by means of tetraiodophenolphthalein. The hormone concentrates (4) upon injection in amounts of 25 to 30 mg. every 10 minutes for one hour in the normal subjects and for 30 minutes in the patients produced some degree of contraction in 4 of the normal subjects and in 2 of the patients; complete emptying

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[1] This study was aided in part by a grant from the National Institutes of Health, Bethesda, Maryland.

occurred in one of the normal subjects. One patient with a pericholecystitis whose gall bladder evacuated partially developed itching, and another patient whose gall bladder did not contract, a chill. The investigation on human subjects was discontinued until a more highly purified preparation could be obtained.

In the present study, gall bladder evacuation was followed in normal human subjects after a single injection of a CCK concentrate, Priodax being used for the visualization of the viscus. Although more potent concentrates of CCK have been produced in this laboratory (5), the present preparation was adopted because it was shown to be free of vasodilatins, allergens, and pyrogen. A few of the subjects were reinjected with the same or a larger dose at a later period. The study was paralleled by experiments on a number of dogs employing the above as well as cruder concentrates, the purpose being to deduce dose-response relationships. In addition. the response to successive doses were carried out on dogs.

EXPERIMENTAL

Preparation of CCK Concentrates

A. SI concentrates. The isolation of these products was affected by treatment of hog duodenal extracts with trichloroacetic acid according to the method of Greengard and Ivy (6). One product (SI-46) included a chloroform treatment step in its preparation leading to a reduced secretin content (5). The preparations were low in vasodilatin.

B. Clinical sample (CCK-100A). The preparation of hormone concentrate used on the human subjects was obtained by further enrichment of SI with aniline according to the Greengard and Ivy procedure, no picrolonic acid being employed in the final stages (5). The dry highly water-soluble product was dissolved in pyrogen-free water, pipetted into vials, and lyophilized. The concentrate which assayed 6.0 units CCK/mg. and 6.0 units secretin/mg. (7) was stored in the cold until used.

TESTING OF CLINICAL SAMPLE. Very small or insignificant blood pressure decreases were noted when 25 mg. of the preparation was injected intravenously into dogs. A rise in the rectal temperature of dogs did not occur after the injection of as much as 40 mg. of the preparation. This showed the absence of pyrogen in the dose to be employed.

Antigenicity was examined by injecting five 250-gm. female guinea pigs subcutaneously with 2.0 mg. of CCK-100A on 3 alternate days. Some sloughing was noted at the site of injection, due to the acid reaction of the aqueous solution. On the 21st day, each was injected intracardially with 4.7 mg. of the product. Although shakiness and incoordination was observed, no anaphylaxis resulted. Similar symptoms occurred with guinea pigs receiving only the intracardial dose. All of the animals survived.

Sterility was tested by the inoculation of Brewer's thioglycolate medium with 1 ml. of an aqueous solution containing 2 mg. of concentrate. No growth was found after an incubation period of 72 hours.

Roentgenological Procedure

A. Dogs. Animals, fasted for 10 to 12 hours, were fed six 0.5-gm. pills of Priodax (Schering) concealed in a small amount of meat at least 15 hours prior

TABLE 1. EFFECT OF INTRAVENOUS INJECTION OF ONE DOSE OF CLINICAL CCK PREPARATION (CCK-100A) ON EVACUATION OF CANINE GALL BLADDER VISUALIZED WITH PRIODAX

DOG (WT., SEX)	TOTAL CCK UNITAGE	GALL BLADDER CONTROL SURFACE AREA	LOWEST POST-INJECTION AREA	SURFACE AREA DECREASE
kg.		*cm.*²	*cm.*²	%
1–15 (12.7, F)	6 (1 mg.)	14.4	13.1	9
2–17 (10.5, M)	6	27.7	27.2	2
4–21 (7.0, M)	6	6.6	6.6	0
5A (11.1, M)	18 (3 mg.)	15.5	12.2	21[1]
6A (11.4, M)	18	11.2	8.5	24
7A (12.0, M)	18	12.2	12.2	0
14 (5.0, M)	36 (6 mg.)	2.7	0	100
1 (14.1, M)	60 (10 mg.)	11.2	7.7	31
2 (13.5, M)	60	7.4	5.2	30
3 (12.5, F)	60	9.0	8.0	11
4 (17.3, M)	60	20.1	18.5	8
6A	60	8.3	6.2	25
7A	60	16.3	12.2	25
9 (16.4, M)	60	8.8	0	100
1–49 (6.8, F)	60	3.1	2.3	26
2–49 (8.9, M)	60	7.9	5.9	25
3–49 (10.7, F)[2]	60	8.3	4.0	52
8 (15.7, F)[3]	150 (25 mg.)	12.6	12.3	2
10 (14.1, M)	150	9.8	0	100
12 (7.5, F)	234 (39 mg.)	6.3	0	100
13 (8.9, M)	240 (40 mg.)	2.8	0	100
15 (13.7, M)	240	15.2	7.6	50

[1] The injection of 60 U (10 mg.) one hour after the first dose of concentrate gave a surface area of 10.4 cm.² or a further decrease of 15%.

[2] Middle stage pregnancy. [3] Very late pregnancy.

to roentgenography. Control films were exposed, and when visualization of the gall bladder was evident, the CCK concentrate was injected within 5 to 15 minutes after the control film. Post-injection films were usually taken at 30- and 60-minute intervals. The dogs were mounted in the same position for control and post-injection filming. A tracing of the contour of each of the gall bladder shadows was made and the respective areas in square centimeters were measured by means of a planimeter. In some animals, successive doses of the hormone concentrate were injected.

B. Humans. The subjects in this series consisted of normal males. On the evening preceding the x-ray examination, 6 to 9 Priodax pills were taken after a light relatively fat-free meal. For skin testing, a very small amount of concentrate in water (less than 0.15 mg.) was injected subcutaneously in the forearm just after the control films were exposed. An aqueous solution of the

TABLE 2. EFFECT OF INTRAVENOUS INJECTION OF ONE DOSE OF SI CCK CONCENTRATES ON EVACUATION OF CANINE GALL BLADDER VISUALIZED WITH PRIODAX

DOG (WT., SEX)	CCK CONCENTRATE[1]	TOTAL CCK UNITAGE	GALL BLADDER CONTROL SURFACE AREA	SMALLEST POST-INJECTION AREA	SURFACE AREA DECREASE
kg.			*cm.*[2]	*cm.*[2]	%
L1 (13.0, F)	SI-46	80 (20 mg.)	18.8	14.2	24
L2 (13.6, M)	SI-46	80	5.2	0	100
L3 (10.9, M)	SI-46	80	8.6	5.5	36
L4 (21.8, F)	SI-46	80	13.2	8.3	37
L5 (16.7, M)	SI-46	80	11.9	7.2	40
	SI-48	80	12.9	6.7	48[3]
L6 (11.8, M)	SI-46	80	9.0	5.5	39
	SI-48	80	7.6	4.6	39
N1 (9.1, F)	SI-86	144 (36 mg.)	11.0	0	100
N2 (9.6, F)	SI-86	144	9.7	4.5	54
N3 (12.3, M)	SI-86	144	9.7	8.4	13
N5 (11.0, M)	SI-86	144	19.7	12.5	37
J1 (9.1, M)	SI-77K	200 (50 mg.)	10.8	6.3	42
	SI-48	200	8.1	5.8	28
J2 (10.9, M)	SI-77K	200	12.4	0	100
	SI-48	200	9.6	8.2	15[3]
J3 (14.0, M)	SI-77K	200	7.4	0	100
	SI-48	200	3.85	0	100
J4 (10.9, M)	SI-77K	200	6.7	3.7	45
	SI-77K	200	9.2	0	100
N4 (16.0, F)	SI-86	300 (75 mg.)	15.0	7.2	52
N8 (11.0, M)	SI-86	400 (100 mg.)	9.6	0	100
N9 (9.5, M)	SI-86	420 (105 mg.)	10.3	0	100

[1] All of the SI concentrates contained 4.0 U CCK/mg. A total of 4.0 U secretin/mg. occurred in each except for SI-46 assaying 2.5 U (modified procedure employing chloroform).

[2] At least 3 to 7 days elapsed before a given dog was retested.

[3] Dog collapsed at the conclusion of the injection, with recovery in 2 minutes.

hormone (2.5–4 ml.) was then injected intravenously and post-injection films were exposed after 30-, 60- and, in some cases, 15-minute intervals. Gall bladder measurements followed. The effect of a fatty meal (Cholex) was also tested radiologically in 3 of the subjects who responded only slightly to the hormone concentrate.

RESULTS

Tables 1 and 2 show the effect on the canine gall bladder of single injections of 6 to 240 CCK units of the clinical product (CCK-100A) and 80 to 420

units as contained in the cruder concentrates (SI), respectively. The latter were also administered in consecutive smaller doses in dogs as indicated in table 3. A maximal evacuation of the gall bladder was achieved within 30 minutes after the injections of various amounts in 4 of the 9 experiments.

The results obtained on the extent of gall bladder evacuation with 18 to 150 CCK units of the clinical preparation in 8 normal human males appear in table 4. The experiments were repeated on 5 of these subjects, 2 receiving the same dose and 3 a higher dose. One subject (*H.R.*) received 18, 66, and 150 units of the CCK concentrate. In all cases, the period of time between tests

TABLE 3. GALL BLADDER EVACUATION AFTER SERIAL INJECTIONS OF SI CCK CONCENTRATES IN DOGS

DOG[1]	PREPARATION	CONTROL AREA	FIRST INJECTION	SURFACE AREA	SECOND INJECTION	SURFACE AREA	THIRD INJECTION	SURFACE AREA	TOTAL SURFACE AREA DECREASE
		*cm.*²	*units*	*cm.*²	*units*	*cm.*²	*units*	*cm.*²	%
J1	SI-77K	8.1	68[1]		68	0.0			100
	SI-4	9.6	68	7.25	68	6.5	68	0.0	100
J3	SI-4	7.9	68	2.6	68	0.0			100
	SI-4	12.7	68	9.0	68	8.1	40	5.7	55
J4	SI-4	8.4	68		68	7.25	68	0.0	100
	SI-77K	11.3	68		68	0.0			100
L5	SI-46	11.0	40	7.6	40	8.0	40	6.3	43
L6	SI-48	12.1	40	10.8	40	12.2	40	8.6	29
	SI-46	9.1	40	4.3	40	0.0			100

[1] Time interval between dosages averaged 15 minutes, films being taken 13 minutes after each injection.

[2] Film is very difficult to read; gall bladder is probably empty.

on a given individual was 6 to 8 months. The gall bladder response of one subject (*R.W.D.*) to 66 units of CCK administered at two different times is shown in figure 1.

The results on the extent of evacuation of the gall bladder to a fatty meal by the 3 subjects who did not evacuate appreciably in response to CCK are shown in table 5.

DISCUSSION

The injection into dogs of single doses of the clinical preparation of CCK resulted in a wide variation of response. In the 10 dogs which received 60 units of CCK or 60 mg. of preparation CCK-100A, the decrease in the shadow of the gall bladder ranged from 8 to 100 per cent. As might be expected the results

show a trend towards a larger degree of evacuation when the dose of CCK is increased (tables 1 and 2). Definite evacuation was achieved with single or successive doses of CCK concentrates.

It is not possible to obtain a quantitative dose-response relationship from the data so far accumulated, since effective contractions were obtained over a

TABLE 4. EFFECT OF SINGLE INTRAVENOUS INJECTION OF CLINICAL CCK PREPARATION (CCK-100A) ON HUMAN GALL BLADDER

CASE[1]	AGE	WEIGHT	HEIGHT	CONTROL SURFACE AREA	LOWEST POST-INJECTION SURFACE AREA	TOTAL SURFACE AREA DECREASE
		kg.	*inches*	*cm.²*	*cm.²*	%
Dosage: 18 units (3.0 mg.)						
1. *H.R.*	30	91	72	25.8	24.0	7
Dosage: 66 units (11 mg.)						
1. *H.R.*				28.9	28.9	0
2. *K.H.*	30	75	70	13.1	9.5	27
2. *K.H.*[2]				23.3	19.3	17
3. *T.K.*	26	60	66	17.7	13.1	26
4. *D.M.*	25	66	71	21.6	19.0	12
5. *R.W.D.*[3]	26	57	65	17.7	0.0	100
6. *R.W.D.*[4]				19.1	13.1	31
Dosage: 150 units (25 mg.)						
1. *H.R.*[5]				17.9	11.2	37
3. *T.K.*[6]				14.9	10.1	32
4. *D.M.*[7]				18.5	17.6	5
6. *H.G.*[8]	23	60	66	18.1	11.2	38
7. *L.L.G.*[8]	31	80	68	19.0	18.6	2
8. *H.M.M.*[9]	35	87	71	25.5	23.0	10

[1] On skin testing, a small subcutaneous injection of CCK-100A gave erythema except in the cases of *T.K.* (Mongoloid) and *H.R.* (Negroid). In the case of *H.M.M.*, a large wheal occurred which decreased in size after 20 minutes.

[2] A small loss in sample occurred at the time of injection. In all cases, the period between tests on the same person was at least 6 months.

[3] This subject who has a seasonal allergy, experienced no ill effects or symptoms except for intense 'hunger pains.'

[4] cf. figure 1.

[5] Blood pressure readings were 140/96 and 150/106 before and 20 minutes after the injection.

[6] Blood pressures before and 20 minutes after the injection were 92/56 and 86/52, respectively.

[7] Blood pressure data: 110/70 and 102/64 before and 20 minutes after the CCK administration, respectively.

[8] Very small or slight flushing.

[9] Definite reaction develops—itching, blood pressure fall; 0.25 ml. 1/1000 adrenaline was administered; this subject was known to be afflicted with seasonal allergic asthma.

wide dosage range. Furthermore, complete duplication of values on retesting a given animal was not always possible.

In the evacuation of the gall bladder in response to CCK several factors other than the amount of CCK in the blood stream are involved (8). Some of the important ones are *a*) the sensitivity and contractility of the musculature of the gall bladder, *b*) the amount and viscosity of the bile in the gall

bladder, *c*) the state of tone of the 'Sphincter of Oddi' or the choledochoduodenal mechanism and its response to CCK and *d*) the extent of CCK inactivation by blood (9, 10). The existence of several such variable factors, especially variations in the tone of the choledochoduodenal mechanism, would mask the occurrence of a strict dose-response relationship. Yet, one should certainly find a trend in that direction, as was observed.

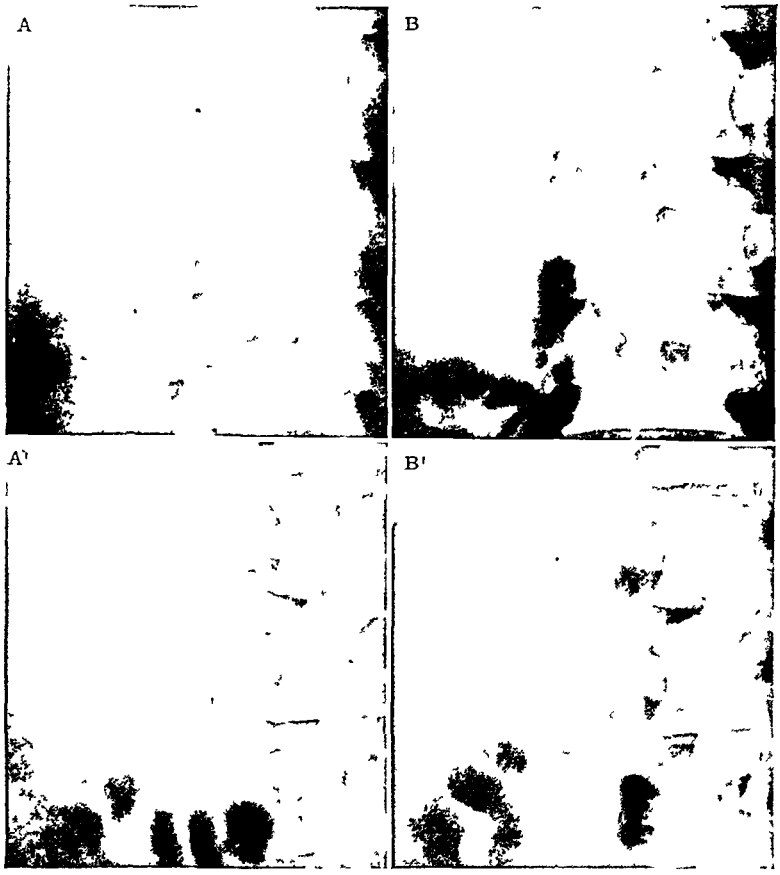

Fig 1 GALL BLADDER EVACUATION in human subject (*R W D*) after CCK *A* Control gall bladder *B* Complete emptying 20 minutes after injection of 66 units CCK-100A *A'* Control *B'*. Contracted gall bladder after administration of same dose of CCK six months later

The results with the human subjects (table 4) are quite striking. Of the 4 receiving 66 units of CCK, one (*R.W D*) emptied completely although several months later in response to the same dosage only a 31 per cent surface-area decrease occurred (fig 1) Two other subjects showed a decrease in size amounting to 27 and 36 per cent, whereas one (*D.M.*) showed little or no emptying with 66 units as well as with 150 units *Subject T K*, who showed a 26 per cent emptying with 66 units, gave about the same amount, namely 32

per cent, when 150 units of CCK was administered six months later. With the latter dosage, a comparable amount of evacuation occurred with 2 other subjects (*H.R.* and *H.G.*), whereas little or no decrease in surface area was observed in 2 of the subjects (*L.L.G.* and *H.M.M.*). The side-reaction developed by *subject H.M.M.* who is highly allergic might have contributed to his poor gall bladder evacuation. *Subject H.R.* responded well with 150 units of CCK, whereas dosages of 18 to 66 units were ineffective.

Although 3 of the cases did not markedly respond to 150 units of CCK, some evacuation (table 5) did result after administration of a fatty meal. This finding, however, does not argue against the possible usefulness of CCK in diagnosis, since the matter of dosage and rate of injection may be involved.

In the present study on humans, single injections of CCK were employed, because this technique, if feasible, would be of greater advantage to both patient and roentgenologist. In view of the rapid inactivation of cholecystokinin

TABLE 5. HUMAN GALL BLADDER CONTRACTION AFTER FATTY MEAL

CASE	CONTROL SURFACE AREA	SURFACE AREA 60 MINUTES AFTER FATTY MEAL[1]	TOTAL SURFACE AREA DECREASE
	*cm.*²	*cm.*²	%
4. *D.M.*	24.4	16.0	34
7. *L.L.G.*	21.9	14.0	36
8. *H.M.M.*	13.4	7.7	43

[1] 30 ml. Cholex (National Synthetics, Inc.).

by body fluids and variations in tone of the Sphincter of Oddi, serial aliquot injections might be more efficacious (9, 10).

It should be noted that in addition to 6.0 units of CCK/mg., 6.0 units of secretin/mg. of concentrate were present. This is mentioned because the choleretic effect of secretin may operate to promote filling of the gall bladder, especially during the second 30-minute post-injection period in the above experiments.

The CCK concentrate (CCK-100A) was non-antigenic to the guinea pig. Some toxic moieties may be present considering the reactions of one allergic subject (table 4).

SUMMARY

A sterile, non-antigenic, pyrogen-free cholecystokinin concentrate has been produced and injected into 8 normal males after gall bladder visualization. With the possible exception of 3 cases, all showed evacuation when 66 or 150 CCK units were administered intravenously in one dose. The injection was repeated several months later in 5 of the subjects who again responded by manifesting some gall bladder evacuation. In dogs a good dose-response rela-

tionship, where the response was the extent of gall bladder evacuation, was not obtained. A trend indicating that the larger the dose the greater the evacuation, was noted. Possible reasons for this are discussed.

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Character of Blood Flow in the Vasodilated Finger[1]

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THE EXTENSION TO THE DIGITS of volume plethysmographic techniques has greatly facilitated studies of digital vascular adjustments. A particular difficulty has been encountered, however, which does not arise in volume plethysmography of other bodily segments. In venous occlusion of markedly vasodilated fingers, levels of blood flow are so high that the volume increase of the part following occlusion is completed within the interval of two or three pulse waves. In such instances it is not possible to apply that method of measurement in which a line is drawn through corresponding points on successive pulse waves following occlusion and its slope is measured. Burton and Taylor (1) have described a method which obviates this difficulty, but which in itself is subject to considerable inaccuracies. In their method the slope of a line drawn tangent to the extrapolated curve of volume increase is measured. Because of the marked variation in duration of volume increase (and hence in the configuration of the extrapolated curve) which occurs with alterations in occlusion pressures, and 'spontaneously' at a given occlusion pressure, it has been found difficult to obtain consistent values by this method.

The possibility that a more accurate method for measurement of high rates of flow in the finger could be derived from slopes of occlusion tracings immediately after occlusion and prior to the onset of 'plateauing' of the tracing stimulated the present work. It was thought, furthermore, that this method might permit a description of the course of blood flow through the finger during the pulse cycle.

The rationale for this approach was developed along the following lines. It was assumed, first of all, that as long as venous outflow is completely obstructed and arterial inflow is unimpeded by increasing pressure within the part, the slope of the volume tracing at any point after occlusion indicates

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[1] This work has been performed in collaboration with the Medical Department, United States Army, which has assigned Medical Corps Officers to the Quartermaster Climatic Research Laboratory for research on adaptations of man to environmental stress.

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the instantaneous rate of arterial flow into the part that would have occurred at that instant independent of occlusion. To the extent that blood is escaping through veins beneath the occlusion cuff, and to the extent that arterial inflow is impeded, the rate determined would fall below arterial flow independent of venous occlusion. Inasmuch as the segment of the occlusion tracing prior to venous 'escape' and impeded arterial flow is of considerably less duration than that of a complete pulse cycle in a vasodilated finger, it would not be possible to determine the average rate of arterial flow from a single tracing. To accomplish this it would be necessary to produce occlusions to cover a sufficient number of segments of separate pulse cycles to permit determination of the course of inflow alteration during the pulse cycle, from which a value for average flow could be derived.

A description of the course of inflow during the pulse cycle would permit also measurement of the variation in outflow from the part during the pulse cycle. The slope of the volume pulse cycle of the finger independent of venous occlusion represents a blood volume rate of change which is the resultant of two separate flow rates: *1*) the rate of flow into the part and *2*) the rate of flow out of the part. When the two rates of flow are equal, the volume rate of change of the part is zero. When the two rates of flow are unequal, the volume rate of change of the part is equal to the difference in the rates of flow. A value for 'instantaneous' rates of outflow may be derived by subtracting, algebraically, the pulse volume slope at a given point from the slope of an occlusion tracing (representing the rate of inflow) at an equivalent point.

In practical application this method presented a number of problems. Inasmuch as only the initial segment of the occlusion tracing was of interest, it was necessary to produce complete venous occlusion within the briefest possible segment of time, and with a minimum of motion of the part. It was also necessary to produce venous occlusions at specific points along the volume pulse cycle, in order to determine the course of flow throughout the pulse cycle. Finally, since these determinations would necessarily be a composite derived from separate pulse cycles, it was necessary to make the observations during periods of relatively constant rates of flow.

METHODS

Volume Recording. A Burch-Winsor Finger Plethysmograph (Cambridge Instrument Co.) was utilized (2). A paper speed of 11.5 cm/sec. was obtained by means of an auxiliary camera motor; this speed was optimal for measurement of the slopes encountered. The adequacy of the plethysmograph for recording volume rates of change throughout the range encountered was checked by the use of an artificial 'finger.' One of the plastic plethysmograph cups was sealed over a 5-cc. portion of a glass tube, the diameter of an average finger. The open end of the tubing within the cup had been covered with a thin rubber

membrane. Water at a 68 mm. Hg pressure head was run into the section of glass tubing through pressure tubing; an outlet ran from the glass tubing through a stop-cock. With the air space within the plethysmograph cup connected by pressure tubing to the volume recorder, water was run through the artificial finger at measured rates. When outflow from the finger was suddenly obstructed, the rubber membrane of the artificial finger distended into the plethysmograph cup. Volume tracings reflecting the increase in volume of the artificial finger were straight lines, the slopes of which were measured and compared with direct measurements of rates of flow through the system. The results are presented in table 1 and demonstrate the adequacy of the instrument for recording volume rates of change over the full range encountered physiologically in this study.

Venous Occlusion Apparatus. Air at 30 pounds/sq.in. pressure was introduced into a reservoir of 300 cc. capacity with an adjustable needle valve outlet permitting control of the pressure within the reservoir. A 6-inch long rubber pressure tube of $\frac{1}{4}$-inch inside diameter ran from the tank to a solenoid operated valve. When the solenoid was energized, air was introduced into a 15-inch length of pressure tubing of $\frac{1}{4}$-inch inside diameter which ran to the occlusion cuff. With the solenoid 'off,' the occlusion cuff was open to the room.

The occlusion cuffs were made in the following manner: 'doughnut'-shaped aluminum forms painted with a coagulant were dipped in natural latex and vulcanized in an oven at 100°C. for 20 minutes. The inner wall of the doughnut was replaced with a loose thin rubber membrane. The doughnuts were individually fitted to fingers with minimal compression. At the pressures utilized (20–40 mm. Hg) the outer wall of the doughnut was little distended, while the thin rubber membrane against the finger compressed the finger without appreciable stretching of the membrane.

In order to measure the speed of pressure transmission to the finger, an indirect method was employed in which the time of deformation of another artificial finger was recorded in the following manner: a metal spool was surrounded with sponge rubber and an outer air-tight thin rubber membrane so that the outer diameter was approximately that of an average finger. The sponge rubber over metal was used in an attempt to approximate the consistency of the finger. The chamber surrounded by the rubber membrane was connected to the volume recorder. An occlusion doughnut was fitted to the artificial finger and connected to the occlusion system. The speed of deformation at a number of occlusion pressures was measured from tracings obtained with the plethysmograph. Deformation was 80 per cent completed within 0.02 second and complete in 0.1 second.

Positioning of the Finger to be Studied. The finger to be studied was supported at heart level on a sand-filled rubber bag which was hardened by an evacuation pump. This technique of support utilizes the principle of dilatancy

(3) and permits a readily molded but firm support which is comfortable for the subject, and at the same time prevents, to a considerable extent, motion of the part. The finger rested on a molded ridge in the sand bag; neither the plethysmograph cup nor the occlusion doughnut was in contact with the support. The plastic plethysmograph cups were sealed with Printer's Roller Compound over the terminal phalanx of the 2nd, 3rd or 4th finger. The volume of the part was measured by overflow technique immediately after each experiment; the mean of at least 5 individual determinations was utilized. The sensitivity of the plethysmograph was adjusted so that a 10-mm. deviation on the tracing represented a 10-cu. mm. change. The occlusion doughnut surrounded the proximal phalanx, the distance between the doughnut and the cup being approximately one inch. It was found necessary to occlude at this distance to avoid occlusion artifact. The possible errors introduced by this condition are evaluated below.

Timing of the Occlusion. The voltage of the electrocardiac cycle was picked up by means of skin electrodes and amplified by a cardiotachometer which selectively modifies and amplifies the QRS complex. The electrical 'pulses' corresponding in time with the QRS complex were passed through a variable time-delay circuit; the output relay of the time-delay circuit was included in the occlusion solenoid circuit. When the time-delay circuit was closed, the next electrical impulse from the cardiotachometer 'fired' a thyratron tube; the output of the tube passed through a resistance-capacitance network. After a delay, which was continuously adjustable between 0.1 second and 2.0 seconds by varying the resistance leg of the R-C network, a second thyratron tube was fired which in turn closed the occlusion solenoid circuit. The occlusion was interrupted by breaking the thyratron circuits. At a given setting, repeated occlusions could be produced at approximately the same point of the volume pulse cycle (within ± 0.05 second). With minimal delays it was possible to establish venous occlusion before the pulse wave (corresponding to the triggering electrocardiac cycle) arrived at the finger; with graded increases of the delay, occlusions could be produced at closely successive points along the volume pulse cycle.

When random coverage of the volume pulse cycle was desired, a simple method of timing was employed. A separate time-delay circuit which afforded independent variation of the 'on' and 'off' phases was connected directly to the occlusion solenoid. With the 'on' phase set for an adequate duration of occlusion, and the 'off' phase set to span approximately 3 pulse cycles, repeated occlusions occurred at random points along the volume pulse cycle.

PROCEDURE

The experiments were performed in a constant temperature room at ambient temperatures of 90° to 95°F. Subjects were 3 healthy young men and one

healthy young woman. They wore light clothing and were comfortably seated with fingers at heart level. In one experiment a subject was further warmed in water at 105°F. to the level of the umbilicus. Tracings with as many as 100 separate occlusions were obtained over periods of 2 or 3 minutes at times when spontaneous variations in finger blood flow were minimal as evidenced by minimal alterations of finger pulse and mean volumes. Fortunately, this important condition is not difficult to attain in individuals near maximal levels of digital vasodilatation, for in this state spontaneous variations in blood flow are small (1).

The possibility that the frequency of venous occlusion might in itself alter blood flow in the finger was investigated by comparing values obtained with varying intervals between occlusions. It was found that occlusions of short duration (approximately that of a single pulse cycle), produced as frequently as every third pulse cycle, yielded average values which were closely similar to average values obtained at greater occlusion intervals.

Methods of Interpretation. Images of the tracings were projected by means of an opaque projector on large white cards. Approximately 50 individual pulse waves taken from the intervals between occlusions were superimposed and traced in pencil on the cards. When a generalized pulse wave had been established, pulse waves with occlusions were superimposed and traced. Slopes of the pulse waves and of the initial segments of the occlusion tracings (covering approximately an 0.04-second segment, beginning 0.04 second after the first deviation) were measured on the composite tracing.

RESULTS AND DISCUSSION

In figure 1 composite tracings obtained in two experiments are presented along with segments of plethysmograph records in which venous occlusion tracings were obtained by what may be called 'standard procedure.' In the first example the subject had been sitting semi-nude in an empty bathtub at an ambient temperature of 95°F. for one hour before the records were obtained. The subject was uncomfortably warm and was sweating moderately, as was evidenced by beads of perspiration forming on his face and forehead. The second tracings were obtained after a 45-minute period of further body warming, accomplished by introducing water into the tub to the level of the umbilicus, the temperature of which was raised to and maintained at 105°F. ± 3°F. During this time the subject became markedly flushed. There were large beads of perspiration over the upper half of his body, his pulse rate had increased from 60–80 to 110–120, and he was conscious of 'pounding' of his heart.

The standard venous occlusion tracings of figure 1 show that, aside from the increase in pulse rate, there is little to distinguish the two records. In contrast are the differences manifested by the composite tracings. The general

features of the composite tracings obtained before and after body heating are similar. In each instance the configuration of individual volume pulses, independent of occlusions, shows remarkably small variation. Occlusion tracings within a given segment have closely similar initial slopes, despite the fact that since their distribution along the pulse cycle was random, they were obtained

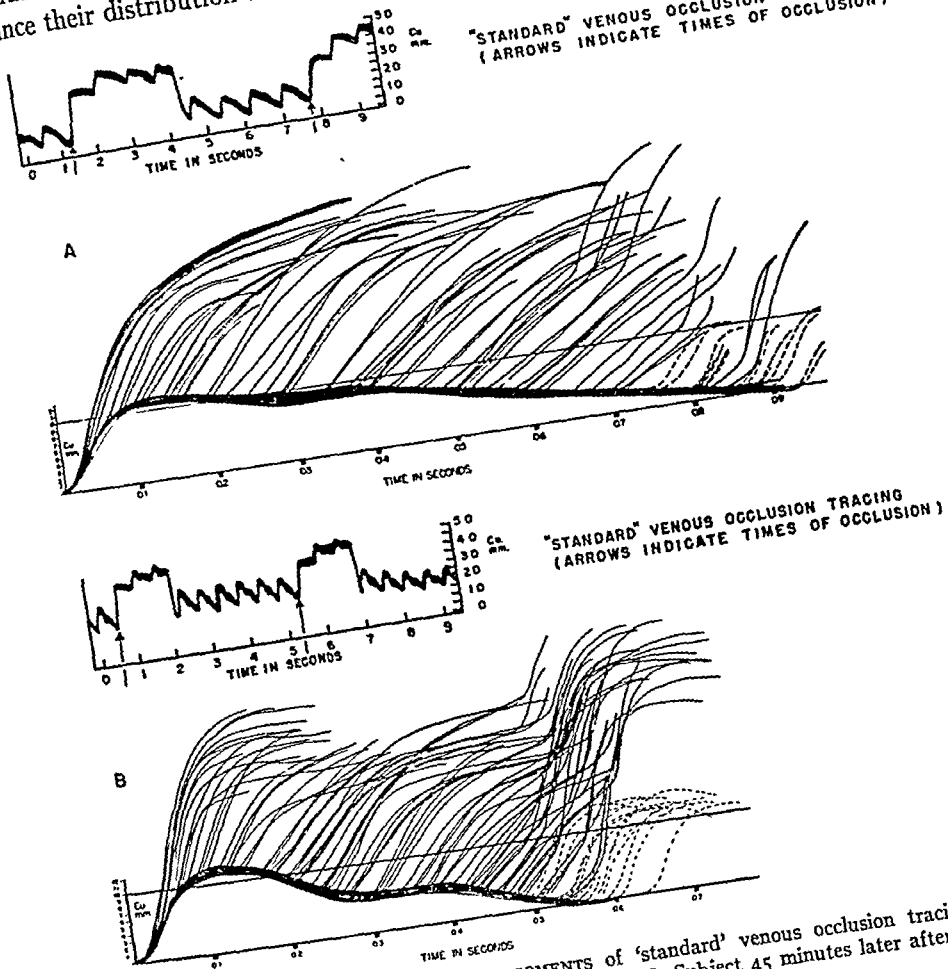


FIG. 1. COMPOSITE TRACINGS AND SEGMENTS of 'standard' venous occlusion tracings. *A:* Subject seated semi-nude at room temperature of 95°F. *B:* Subject 45 minutes later after further body heating in a water bath at 105° F.

separately at intervals of as much as 2 minutes. There are no abrupt discontinuities during the initial portions of the occlusion tracings, and no occlusion artifact is obvious.

Features distinguishing the composite tracings before and after body heating may be seen both in the volume pulse configuration and in the slopes of the occlusion tracings. After body heating, although the volume pulse am-

plitude is only slightly increased, the configuration of the pulse wave differs from the preheating configuration in the steepness of the initial volume increase, in the 'depth' of the dicrotic notch and, of course, in the duration of the cycle. The slopes of the individual occlusion tracings are considerably greater throughout the pulse cycle in the tracings obtained after heating.

In figure 2 measurements made directly from the composite tracings are plotted. The observed variations in finger volume (independent of occlusion), finger volume rate of change (independent of occlusion), absolute finger volume rate of change initially following occlusions (rate of inflow), and the algebraic difference between initial occlusion slopes and corresponding volume pulse slopes (rate of outflow) are presented. In both instances inflow rises abruptly to maximal levels at a point corresponding to the maximal rate of finger volume increase; thereafter it falls abruptly, rises somewhat in the segment of the dicrotic notch and then falls more gradually to minimal levels at the end of the pulse cycle. The values calculated for outflow rise less abruptly to maximal levels at about the time of maximal absolute finger volume; during the phase of finger pulse volume decrease outflow remains higher than inflow, falling gradually to minimal values at the end of the cycle. The curves of inflow and outflow intercept at the points of minimal and again at maximal finger volume.

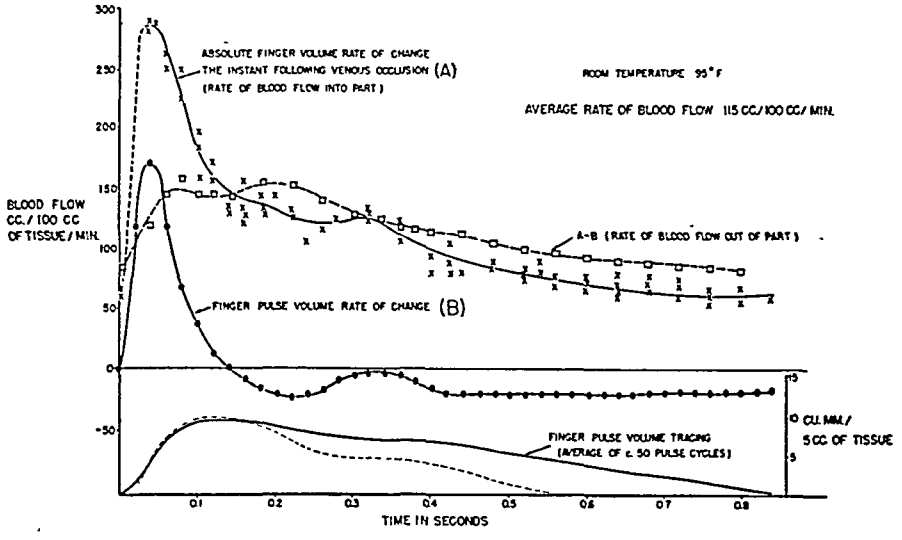
Before heating, the total variation in the rate of inflow was from 60 to 290 cc/100 cc. of tissue/min. After heating, the range was 120 to 400 cc/100 cc/min. Ranges for outflow before and after heating were: 90 to 150 cc/100 cc/min. before, and 150 to 240 cc/100 cc/min. after body heating.

Mean values for inflow, representing the average rate of blood flow through the part, were obtained by measuring the areas under the curves of inflow. The means of outflow, of course, gave the same values since absolute finger volume did not change appreciably during the tests. Before body heating the average rate of flow through the finger was calculated to be 115 cc/100 cc/min.; after body heating the average rate of flow had risen to 173 cc/100 cc/min. Table 2 presents minimal, maximal and mean values for inflow and outflow obtained in 5 subjects (including the initial values on *Subject A*) observed under conditions similar to the 'before body heating' illustration. The patterns of the composite tracings obtained were similar to those presented above.

In evaluating the results obtained, possible sources of artifact have been considered as follows:

1) *Artifacts Introduced by Non-linearity of the Volume Recording System.* The adequacy of the volume recording system for recording volume rates of change over the range encountered physiologically was demonstrated by the procedure described in *Methods*.

2) *Occlusion Cuff Artifacts.* The fact that when repeated occlusions were produced at any given point on the pulse cycle, occlusion pressures could be



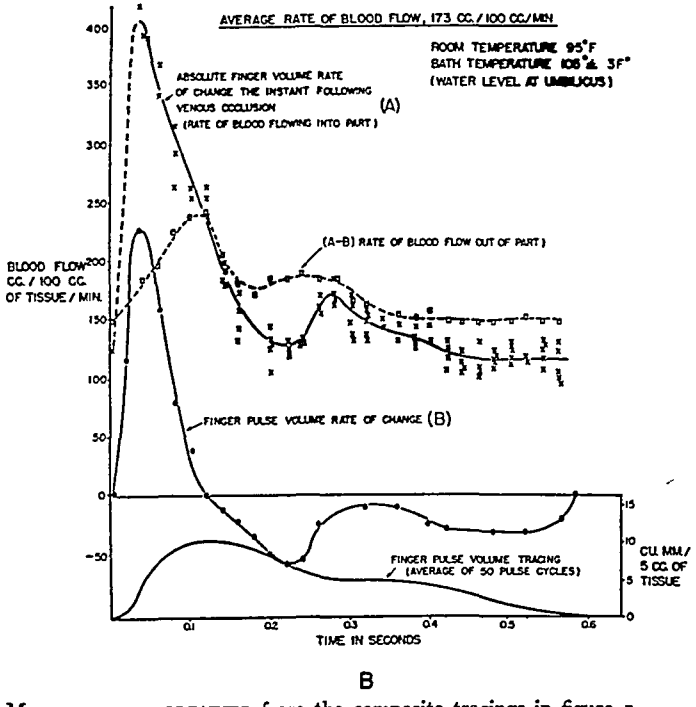


FIG. 2. MEASUREMENTS OBTAINED from the composite tracings in figure 1.

varied as much as 25 mm. Hg without influencing the initial slopes, has been taken as evidence that *a*) venous occlusion is complete throughout this segment; *b*) arterial inflow is not impeded by the direct effect of the occlusion

cuff; and *c*) 'cuff artifact', i.e. volume changes due to motion of tissue into or out of the plethysmograph cup, is negligible. Additional evidence of the absence of occlusion artifact was obtained by showing that 'occlusions' produced no volume change in arterially occluded fingers. Furthermore, with intact circulation, no artifact was observed at low rates of blood flow, when the volume increase following occlusion was as little as one mm. in 5 cm. of record.

3) Limitations Introduced by the Distance of the Occlusion Cuff from the Inclosed Part. While placement of the occlusion cuff at the level of the proximal phalanx permitted the necessary freedom from cuff artifact, it at the same time introduced a considerable limitation in interpreting the results. To the extent that venous blood 'escaped' from the inclosed terminal phalanx to the uninclosed middle phalanx, recorded flows deviated below actual terminal phalangeal flows. To investigate the extent of this effect 2 occlusion cuffs were employed. One was placed at a distance of $\frac{1}{4}$- to $\frac{1}{2}$-inch from the cup, so that

TABLE 1

Directly Measured Rates of Flow

14	60	80	88	156	182	200	300	336	380	384	456	460
Rates of Flow Measured from Tracings												
14	62	80	89	160	186	204	334	344	410	412	480	480

Rates of flow as expressed are equivalent to cc/100 cc. tissue/min.

the intervening distance was as small as practicably possible. The other surrounded the proximal phalanx at a distance of one inch to one and one-half inches from the cup. High rates of flow could not be compared for the very reason that the more proximal cuff had been utilized in the remainder of the studies (i.e. cuff artifact produced by the distal cuff prevented accurate measurement). However, over a range from 5 cc. to approximately 70 cc/100 cc/min. satisfactory measurements could be made with the distal cup. When averages of approximately 100 such flows obtained alternately with the 2 cuffs over a period of about 5 minutes were compared in 2 individuals observed on 3 occasions each, average flows with the distal cuff ranged from 50 to 200 per cent higher than proximal cuff flows.

Mean flows recorded in this report, therefore, are not 'true' flows through the terminal phalanx, but rather represent intermediate values lying between the rate of flow through the entire digit distal to the occlusion cuff and that through the inclosed terminal phalanx. The fact that percentage differences between proximal and distal cuff flows did not alter measurably for a given

individual over the range of flows studied, suggests that a similar difference may exist at maximal flows, and that true flows through the inclosed part may be as much as 3 times the magnitude of those recorded in this paper. Furthermore, if it may be assumed that the rate of venous escape from the inclosed to the uninclosed segment of the digit is greatest during the phase of maximal calculated venous flow, the true extent of venous and arterial flow variation during the pulse cycle is greater than the recorded variation.

4) Possibility of Arterial Back-flow. An assumption that 'outflow' from the digit is entirely through veins is subject to question by a finding of Wright and Phelps (4). In studies of blood flow in the calf and foot, utilizing a very sensitive air plethysmograph, they noted negative slopes during the late systolic phase of pulse cycles following venous occlusion, and concluded that this represented arterial back-flow produced by transient reversals of the pressure gradient between the larger arteries and the more peripheral vessels. This phenomenon did not occur at high flows. Under the conditions presented

TABLE 2. RATES OF DIGITAL BLOOD FLOW IN CC/100 CC/MIN.

SUBJECT	SEX	MEAN FLOW	MAXIMAL INFLOW	MINIMAL INFLOW	MAXIMAL OUTFLOW	MINIMAL OUTFLOW
A	Male	115	290	60	150	90
B	Male	133	275	70	183	90
C	Male	126	200	75	158	90
D	Male	142	280	100	190	118
E	Female	138	309	58	222	98

here, phases of arterial backflow were never observed, as evidenced by the consistently positive slopes of the occlusion tracings. Hence, 'inflow' is considered to be arterial, and 'outflow,' venous.

In conclusion, it may be stated that in the vasodilated finger venous blood flow is markedly pulsatile. Average levels of flow through the terminal phalanges are at least as high as the values recorded, and may be considerably higher. If 150 cc/100 cc/min. be near maximal flow through the terminal phalanx, and 30 cc/100 cc/min., a comparable value for the entire hand, at least 35 per cent of the maximally vasodilated hand's blood flow is through the 5 terminal phalanges, which represent approximately 5 per cent of the volume of the hand and 19 per cent of its surface area. The hypothesis that flow through the arteriovenous shunts known to be present in the digit accounts for the high flow observed in the digits is an attractive one which has received some experimental confirmation in the skin temperature studies of Grant and Bland (5, 6). The finding of pulsatile venous flow in the vasodilated finger lends further support to this hypothesis.

SUMMARY AND CONCLUSIONS

A method is described for the determination of instantaneous rates of arterial and venous flow through the fingers from measurements of volume plethysmographic venous occlusion tracings. In vasodilated fingers, both arterial and venous flow have been shown to be markedly pulsatile in character during the course of the pulse cycle. Values for mean rates of blood flow through the finger are derived from measurements of the areas under the curves of arterial or venous blood flow alteration throughout pulse cycle. In 5 individuals seated in an uncomfortably warm environment, mean flow ranged from 115 cc. to 142 cc/100 cc. tissue/min. In one individual, further warmed in a bath tub, a mean value of 173 cc/100 cc/min. was obtained. Evidence is presented which suggests that actual mean rates of flow through the terminal phalanx exceed these values 2- to 3-fold. The pulsatile character of venous flow in the vasodilated finger is consistent with flow through arteriovenous shunts known to be present in the finger.

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